



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/US98/00449  <b>(22) International Filing Date:</b> 7 January 1998 (07.01.98)  <b>(30) Priority Data:</b> 60/034,905      7 January 1997 (07.01.97)      US 60/055,404      8 August 1997 (08.08.97)      US 60/066,029      14 November 1997 (14.11.97)      US 60/065,442      14 November 1997 (14.11.97)      US  <b>(71) Applicant:</b> AMYLIN PHARMACEUTICALS, INC. [US/US]; 9373 Towne Centre Drive, San Diego, CA 92121 (US).  <b>(72) Inventors:</b> BEELEY, Nigel, Robert, Arnold; 227 Loma Corta Drive, Solana Beach, CA 92075 (US). PRICKETT, Kathryn, S.; 7612 Trailbrush Terrace, San Diego, CA 92126 (US). BHAVSAR, Sunil; Apartment #7, 917 Torrance Street, San Diego, CA 92103 (US).  <b>(74) Agents:</b> DUFT, Bradford, J. et al.; Lyon & Lyon LLP, First Interstate World Center, Suite 4700, 633 West Fifth Street, Los Angeles, CA 90071 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i>
<b>(54) Title:</b> USE OF EXENDINS AND AGONISTS THEREOF FOR THE REDUCTION OF FOOD INTAKE  <b>(57) Abstract</b>  <p>Methods for treating conditions or disorders which can be alleviated by reducing food intake are disclosed which comprise administration of an effective amount of an exendin or an exendin agonist, alone or in conjunction with other compounds or compositions that effect satiety. The methods are useful for treating conditions or disorders, including obesity, Type II diabetes, eating disorders, and insulin-resistance syndrome. The methods are also useful for lowering the plasma glucose level, lowering the plasma lipid level, reducing the cardiac risk, reducing the appetite, and reducing the weight of subjects. Pharmaceutical compositions for use in the methods of the invention are also disclosed.</p>		

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USE OF EXENDINS AND AGONISTS THEREOF  
FOR THE REDUCTION OF FOOD INTAKE

This application claims the benefit of U.S. Provisional Application No. 60/034,905, filed January 7, 1997, U.S. Provisional Application No. 60/055,404, filed August 8, 1997, U.S. Provisional Application No. 60/066,029  
5 filed November 14, 1997, and U.S. Provisional Application No. 60/065,442, November 14, 1997.

FIELD OF THE INVENTION

10 The present invention relates to methods for treating conditions or disorders which can be alleviated by reducing food intake comprising administration of an effective amount of an exendin or an exendin agonist alone or in conjunction with other compounds or compositions that  
15 affect satiety such as a leptin or an amylin agonist. The methods are useful for treating conditions or disorders, in which the reduction of food intake is of value, including obesity, Type II diabetes, eating disorders, and insulin-resistance syndrome. The methods are also useful for  
20 lowering the plasma lipid level, reducing the cardiac risk, reducing the appetite, and reducing the weight of subjects. Pharmaceutical compositions for use in the methods of the

invention are also disclosed.

#### BACKGROUND

5 The following description summarizes information relevant to the present invention. It is not an admission that any of the information provided herein is prior art to the presently claimed invention, nor that any of the publications specifically or implicitly referenced are prior art to that invention.

#### 10 Exendin

Exendins are peptides that are found in the venom of the Gila-monster, a lizard found in Arizona, and the Mexican Beaded Lizard. Exendin-3 is present in the venom of Heloderma horridum, and exendin-4 is present in the  
15 venom of Heloderma suspectum (Eng, J., et al., J. Biol. Chem., 265:20259-62, 1990; Eng., J., et al., J. Biol. Chem., 267:7402-05, 1992). The exendins have some sequence similarity to several members of the glucagon-like peptide family, with the highest homology, 53%, being to GLP-1[7-  
20 36]NH<sub>2</sub> (Goke, et al., J. Biol. Chem., 268:19650-55, 1993). GLP-1[7-36]NH<sub>2</sub>, also known as proglucagon[78-107], has an insulinotropic effect, stimulating insulin secretion from pancreatic  $\beta$ -cells; GLP also inhibits glucagon secretion from pancreatic  $\alpha$ -cells (Orskov, et al., Diabetes, 42:658-  
25 61, 1993; D'Alessio, et al., J. Clin. Invest., 97:133-38,



1996). GLP-1 is reported to inhibit gastric emptying (Williams B, et al., J Clin Endocrinol Metab 81 (1): 327-32, 1996; Wettergren A, et al., Dig Dis Sci 38 (4): 665-73, 1993), and gastric acid secretion. (Schjoldager BT, et al., Dig Dis Sci 34 (5): 703-8, 1989; O'Halloran DJ, et al., J Endocrinol 126 (1): 169-73, 1990; Wettergren A, et al., Dig Dis Sci 38 (4): 665-73, 1993). GLP-1[7-37], which has an additional glycine residue at its carboxy terminus, also stimulates insulin secretion in humans (Orskov, et al., Diabetes, 42:658-61, 1993). A transmembrane G-protein adenylate-cyclase-coupled receptor believed to be responsible for the insulinotropic effect of GLP-1 is reported to have been cloned from a  $\beta$ -cell line (Thorens, Proc. Natl. Acad. Sci. USA 89:8641-45 (1992)).

Exendin-4 potently binds at GLP-1 receptors on insulin-secreting  $\beta$ TC1 cells, at dispersed acinar cells from guinea pig pancreas, and at parietal cells from stomach; the peptide is also said to stimulate somatostatin release and inhibit gastrin release in isolated stomachs (Goke, et al., J. Biol. Chem. 268:19650-55, 1993; Schepp, et al., Eur. J. Pharmacol., 69:183-91, 1994; Eissele, et al., Life Sci., 55:629-34, 1994). Exendin-3 and exendin-4 were reported to stimulate cAMP production in, and amylase release from, pancreatic acinar cells (Malhotra, R., et al., Regulatory Peptides, 41:149-56, 1992; Raufman, et al.,

J. Biol. Chem. 267:21432-37, 1992; Singh, et al., Regul. Pept. 53:47-59, 1994). The use of exendin-3 and exendin-4 as insulinotrophic agents for the treatment of diabetes mellitus and the prevention of hyperglycemia has been  
5 proposed (Eng, U.S. Patent No. 5,424,286).

C-terminally truncated exendin peptides such as exendin[9-39], a carboxyamidated molecule, and fragments 3-39 through 9-39 have been reported to be potent and selective antagonists of GLP-1 (Goke, et al., J. Biol. Chem., 268:19650-55, 1993; Raufman, J.P., et al., J. Biol. Chem. 266:2897-902, 1991; Schepp, W., et al., Eur. J. Pharm. 269:183-91, 1994; Montrose-Rafizadeh, et al., Diabetes, 45(Suppl. 2):152A, 1996). Exendin[9-39] is said  
10 to block endogenous GLP-1 in vivo, resulting in reduced insulin secretion. Wang, et al., J. Clin. Invest., 95:417-21, 1995; D'Alessio, et al., J. Clin. Invest., 97:133-38, 1996). The receptor apparently responsible for the insulinotropic effect of GLP-1 has reportedly been cloned from rat pancreatic islet cell (Thorens, B., Proc. Natl. Acad. Sci. USA 89:8641-8645, 1992).  
20 Exendins and exendin[9-39] are said to bind to the cloned GLP-1 receptor (rat pancreatic  $\beta$ -cell GLP-1 receptor (Fehmann HC, et al., Peptides 15 (3): 453-6, 1994) and human GLP-1 receptor (Thorens B, et al., Diabetes 42 (11): 1678-82, 1993). In  
25 cells transfected with the cloned GLP-1 receptor, exendin-4

is reportedly an agonist, i.e., it increases cAMP, while exendin[9-39] is identified as an antagonist, i.e., it blocks the stimulatory actions of exendin-4 and GLP-1. Id.

Exendin[9-39] is also reported to act as an antagonist of the full length exendins, inhibiting stimulation of pancreatic acinar cells by exendin-3 and exendin-4 (Raufman, et al., J. Biol. Chem. 266:2897-902, 1991; Raufman, et al., J. Biol. Chem., 266:21432-37, 1992). It is also reported that exendin[9-39] inhibits the stimulation of plasma insulin levels by exendin-4, and inhibits the somatostatin release-stimulating and gastrin release-inhibiting activities of exendin-4 and GLP-1 (Kolligs, F., et al., Diabetes, 44:16-19, 1995; Eissele, et al., Life Sciences, 55:629-34, 1994).

Exendins have recently been found to inhibit gastric emptying (U.S.S.N. 08/694,954, filed August 8, 1996, which enjoys common ownership with the present invention and is hereby incorporated by reference).

Exendin [9-39] has been used to investigate the physiological relevance of central GLP-1 in control of food intake (Turton, M.D. et al. Nature 379:69-72, 1996). GLP-1 administered by intracerebroventricular injection inhibits food intake in rats. This satiety-inducing effect of GLP-1 delivered ICV is reported to be inhibited by ICV injection of exendin [9-39] (Turton, supra). However, it has been

reported that GLP-1 does not inhibit food intake in mice when administered by peripheral injection (Turton, M.D., Nature 379:69-72, 1996; Bhavsar, S.P., Soc. Neurosci. Abstr. 21:460 (188.8), 1995).

5                                    Obesity and Hypernutrition

Obesity, excess adipose tissue, is becoming increasingly prevalent in developed societies. For example, approximately 30% of adults in the U.S. were estimated to be 20 percent above desirable body weight --  
10    an accepted measure of obesity sufficient to impact a health risk (*Harrison's Principles of Internal Medicine* 12th Edition, McGraw Hill, Inc. (1991) p. 411). The pathogenesis of obesity is believed to be multifactorial but the basic problem is that in obese subjects food intake  
15    and energy expenditure do not come into balance until there is excess adipose tissue. Attempts to reduce food intake, or hypernutrition, are usually fruitless in the medium term because the weight loss induced by dieting results in both increased appetite and decreased energy expenditure (Leibel  
20    et al., (1995) *New England Journal of Medicine* 322: 621-628). The intensity of physical exercise required to expend enough energy to materially lose adipose mass is too great for most people to undertake on a sufficiently frequent basis. Thus, obesity is currently a poorly  
25    treatable, chronic, essentially intractable metabolic

disorder. Not only is obesity itself believed by some to be undesirable for cosmetic reasons, but obesity also carries serious risk of co-morbidities including, Type 2 diabetes, increased cardiac risk, hypertension, atherosclerosis, degenerative arthritis, and increased incidence of complications of surgery involving general anesthesia. Obesity due to hypernutrition is also a risk factor for the group of conditions called insulin resistance syndrome, or "syndrome X." In syndrome X, it has been reported that there is a linkage between insulin resistance and hypertension. (Watson N. and Sandler M., *Curr. Med. Res. Opin.*, 12(6):374-378 (1991); Kodama J. et al., *Diabetes Care*, 13(11):1109-1111 (1990); Lithell et al., *J. Cardiovasc. Pharmacol.*, 15 Suppl. 5:S46-S52 (1990)).

In those few subjects who do succeed in losing weight, by about 10 percent of body weight, there can be striking improvements in co-morbid conditions, most especially Type 2 diabetes in which dieting and weight loss are the primary therapeutic modality, albeit relatively ineffective in many patients for the reasons stated above. Reducing food intake in obese subjects would decrease the plasma glucose level, the plasma lipid level, and the cardiac risk in these subjects. Hypernutrition is also the result of, and the psychological cause of, many eating disorders.

Reducing food intake would also be beneficial in the treatment of such disorders.

Thus, it can be appreciated that an effective means to reduce food intake is a major challenge and a superior method of treatment would be of great utility. Such a method, and compounds and compositions which are useful therefor, have been invented and are described and claimed herein.

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#### SUMMARY OF THE INVENTION

The present invention concerns the surprising discovery that exendins and exendin agonists have a profound and prolonged effect on inhibiting food intake.

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The present invention is directed to novel methods for treating conditions or disorders associated with hypernutrition, comprising the administration of an exendin, for example, exendin-3 [SEQ ID NO. 1: His Ser Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser], or exendin-4 [SEQ ID NO. 2: His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser], or other compounds which effectively bind to the receptor at which exendin exerts its

action on reducing food intake. These methods will be useful in the treatment of, for example, obesity, diabetes, including Type II or non-insulin dependent diabetes, eating disorders, and insulin-resistance syndrome.

5 In a first aspect, the invention features a method of treating conditions or disorders which can be alleviated by reducing food intake in a subject comprising administering to the subject a therapeutically effective amount of an exendin or an exendin agonist. By an "exendin agonist" is  
10 meant a compound that mimics the effects of exendin on the reduction of food intake by binding to the receptor or receptors where exendin causes this effect. Preferred exendin agonist compounds include those described in United States Provisional Patent Application Serial No. 60/055,404,  
15 entitled, "Novel Exendin Agonist Compounds," filed August 8, 1997; United States Provisional Patent Application Serial No. 60/065,442, entitled, "Novel Exendin Agonist Compounds," filed November 14, 1997; and United States Provisional Patent Application Serial No. 60/066,029, entitled, "Novel  
20 Exendin Agonist Compounds," filed November 14, 1997; all of which enjoy common ownership with the present application and all of which are incorporated by this reference into the present application as though fully set forth herein. By "condition or disorder which can be alleviated by reducing  
25 food intake" is meant any condition or disorder in a subject

that is either caused by, complicated by, or aggravated by a relatively high food intake, or that can be alleviated by reducing food intake. Such conditions or disorders include, but are not limited to, obesity, diabetes, including Type II  
5 diabetes, eating disorders, and insulin-resistance syndrome.

Thus, in a first embodiment, the present invention provides a method for treating conditions or disorders which can be alleviated by reducing food intake in a subject comprising administering to said subject a therapeutically  
10 effective amount of an exendin or an exendin agonist. Preferred exendin agonist compounds include those described in U.S. Provisional Patent Application Serial Nos. 60/055,404; 60/065,442; and 60/066,029, which have been incorporated by reference in the present application.

15 Preferably, the subject is a vertebrate, more preferably a mammal, and most preferably a human. In preferred aspects, the exendin or exendin agonist is administered parenterally, more preferably by injection. In a most preferred aspect, the injection is a peripheral injection. Preferably, about  
20 10  $\mu$ g-30  $\mu$ g to about 5 mg of the exendin or exendin agonist is administered per day. More preferably, about 10-30  $\mu$ g to about 2mg, or about 10-30  $\mu$ g to about 1mg of the exendin or exendin agonist is administered per day. Most preferably, about 30  $\mu$ g to about 500  $\mu$ g of the exendin or exendin  
25 agonist is administered per day.



In various preferred embodiments of the invention, the condition or disorder is obesity, diabetes, preferably Type II diabetes, an eating disorder, or insulin-resistance syndrome.

5 In other preferred aspects of the invention, a method is provided for reducing the appetite of a subject comprising administering to said subject an appetite-lowering amount of an exendin or an exendin agonist.

10 In yet other preferred aspects, a method is provided for lowering plasma lipids comprising administering to said subject a therapeutically effective amount of an exendin or an exendin agonist.

The methods of the present invention may also be used to reduce the cardiac risk of a subject comprising  
15 administering to said subject a therapeutically effective amount of an exendin or an exendin agonist. In one preferred aspect, the exendin or exendin agonist used in the methods of the present invention is exendin-3. In another preferred aspect, said exendin is exendin-4. Other  
20 preferred exendin agonists include exendin-4 (1-30) [SEQ ID NO 6: His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly], exendin-4 (1-30) amide [SEQ ID NO 7: His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala  
25 Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly-NH<sub>2</sub>],

exendin-4 (1-28) amide [SEQ ID NO 40: His Gly Glu Gly Thr  
Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg  
Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>], <sup>14</sup>Leu,<sup>25</sup>Phe exendin-4  
amide [SEQ ID NO 9: His Gly Glu Gly Thr Phe Thr Ser Asp Leu  
5 Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe  
Leu Lys Asn Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser-NH<sub>2</sub>],  
<sup>14</sup>Leu,<sup>25</sup>Phe exendin-4 (1-28) amide [SEQ ID NO 41: His Gly Glu  
Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala  
Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>], and  
10 <sup>14</sup>Leu,<sup>22</sup>Ala,<sup>25</sup>Phe exendin-4 (1-28) amide [SEQ ID NO 8: His Gly  
Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu  
Ala Val Arg Leu Ala Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>].

In the methods of the present invention, the exendins  
and exendin agonists may be administered separately or  
15 together with one or more other compounds and compositions  
that exhibit a long term or short-term satiety action,  
including, but not limited to other compounds and  
compositions that comprise an amylin agonist,  
cholecystokinin (CCK), or a leptin (ob protein). Suitable  
20 amylin agonists include, for example, [<sup>25,28,29</sup>Pro-]-human  
amylin (also known as "pramlintide," and previously referred  
to as "AC-137") as described in "Amylin Agonist Peptides and  
Uses Therefor," U.S. Patent No. 5,686,511, issued November  
11, 1997, and salmon calcitonin. The CCK used is preferably  
25 CCK octopeptide (CCK-8). Leptin is discussed in, for

example, Pelleymounter, M.A., et al. Science 269:540-43 (1995); Halaas, J.L., et al. Science 269:543-46 (1995); and Campfield, L.A., et al. Eur. J. Pharmac. 262:133-41 (1994).

5 In other embodiments of the invention is provided a pharmaceutical composition for use in the treatment of conditions or disorders which can be alleviated by reducing food intake comprising a therapeutically effective amount of an exendin or exendin agonist in association with a pharmaceutically acceptable carrier. Preferably, the  
10 pharmaceutical composition comprises a therapeutically effective amount for a human subject.

The pharmaceutical composition may preferably be used for reducing the appetite of a subject, reducing the weight of a subject, lowering the plasma lipid level of a subject,  
15 or reducing the cardiac risk of a subject. Those of skill in the art will recognize that the pharmaceutical composition will preferably comprise a therapeutically effective amount of an exendin or exendin agonist to accomplish the desired effect in the subject.

20 The pharmaceutical compositions may further comprise one or more other compounds and compositions that exhibit a long-term or short-term satiety action, including, but not limited to other compounds and compositions that comprise an amylin agonist, CCK, preferably CCK-8, or leptin. Suitable  
25 amylin agonists include, for example, [<sup>25,28,29</sup>Pro]-human amylin

and salmon calcitonin.

In one preferred aspect, the pharmaceutical composition comprises exendin-3. In another preferred aspect, the pharmaceutical composition comprises exendin-4. In other preferred aspects, the pharmaceutical compositions comprises a peptide selected from: exendin-4 (1-30), exendin-4 (1-30) amide, exendin-4 (1-28) amide, <sup>14</sup>Leu,<sup>25</sup>Phe exendin-4 amide, <sup>14</sup>Leu,<sup>25</sup>Phe exendin-4 (1-28) amide, and <sup>14</sup>Leu,<sup>22</sup>Ala,<sup>25</sup>Phe exendin-4 (1-28) amide.

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#### BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graphical depiction of the change of food intake in normal mice after intraperitoneal injection of exendin-4 and GLP-1.

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Figure 2 is a graphical depiction of the change of food intake in obese mice after intraperitoneal injection of exendin-4.

Figure 3 is a graphical depiction of the change of food intake in rats after intracerebroventricular injection of exendin-4

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Figure 4 is a graphical depiction of the change of food intake in normal mice after intraperitoneal injection of exendin-4 (1-30) ("Compound 1").

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Figure 5 is a graphical depiction of the change of food

intake in normal mice after intraperitoneal injection of  
exendin-4 (1-30) amide ("Compound 2").

Figure 6 is a graphical depiction of the change of food  
intake in normal mice after intraperitoneal injection of  
5 exendin-4 (1-28) amide ("Compound 3").

Figure 7 is a graphical depiction of the change of food  
intake in normal mice after intraperitoneal injection of  
<sup>14</sup>Leu, <sup>25</sup>Phe exendin-4 amide ("Compound 4").

Figure 8 is a graphical depiction of the change of food  
10 intake in normal mice after intraperitoneal injection of  
<sup>14</sup>Leu, <sup>25</sup>Phe exendin-4 (1-28) amide ("Compound 5").

Figure 9 is a graphical depiction of the change of food  
intake in normal mice after intraperitoneal injection of  
<sup>14</sup>Leu, <sup>22</sup>Ala, <sup>25</sup>Phe exendin-4 (1-28) amide ("Compound 6").

15 Figure 10 depicts the amino acid sequences for certain  
exendin agonist compounds useful in the present invention  
[SEQ ID NOS 9-39].

#### DETAILED DESCRIPTION OF THE INVENTION

20 Exendins and exendin agonists are useful as described  
herein in view of their pharmacological properties.  
Activity as exendin agonists can be indicated by activity in  
the assays described below. Effects of exendins or exendin  
agonists on reducing food intake can be identified,  
25 evaluated, or screened for, using the methods described in

the Examples below, or other methods known in the art for determining effects on food intake or appetite.

### Exendin Agonist Compounds

5

Exendin agonist compounds are those described in U.S. Provisional Application No. 60/055,404, including compounds of the formula (I) [SEQ ID NO. 3]:

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      1               5               10
Xaa1 Xaa2 Xaa3 Gly Thr Xaa4 Xaa5 Xaa6 Xaa7 Xaa8
              15               20
Ser Lys Gln Xaa9 Glu Glu Glu Ala Val Arg Leu
      25               30
15 Xaa10 Xaa11 Xaa12 Xaa13 Leu Lys Asn Gly Gly Xaa14
              35
Ser Ser Gly Ala Xaa15 Xaa16 Xaa17 Xaa18-Z

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wherein Xaa<sub>1</sub> is His, Arg or Tyr; Xaa<sub>2</sub> is Ser, Gly, Ala or Thr; Xaa<sub>3</sub> is Asp or Glu; Xaa<sub>4</sub> is Phe, Tyr or naphthylalanine; Xaa<sub>5</sub> is Thr or Ser; Xaa<sub>6</sub> is Ser or Thr; Xaa<sub>7</sub> is Asp or Glu; Xaa<sub>8</sub> is Leu, Ile, Val, pentylglycine or Met; Xaa<sub>9</sub> is Leu, Ile, pentylglycine, Val or Met; Xaa<sub>10</sub> is Phe, Tyr or naphthylalanine; Xaa<sub>11</sub> is Ile, Val, Leu, pentylglycine, tert-butylglycine or Met; Xaa<sub>12</sub> is Glu or Asp; Xaa<sub>13</sub> is Trp, Phe, Tyr, or naphthylalanine; Xaa<sub>14</sub>, Xaa<sub>15</sub>, Xaa<sub>16</sub> and Xaa<sub>17</sub> are independently Pro, homoproline, 3Hyp, 4Hyp, thioproline, N-alkylglycine, N-alkylpentylglycine or N-alkylalanine; Xaa<sub>18</sub> is Ser, Thr or Tyr; and Z is -OH or -NH<sub>2</sub>; with the proviso that the compound is not exendin-3 or

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exindin-4.

Preferred N-alkyl groups for N-alkylglycine, N-alkylpentylglycine and N-alkylalanine include lower alkyl groups preferably of 1 to about 6 carbon atoms, more preferably of 1 to 4 carbon atoms. Suitable compounds include those listed in Figure 10 having amino acid sequences of SEQ. ID. NOS. 9 to 39.

Preferred exendin agonist compounds include those wherein Xaa<sub>1</sub> is His or Tyr. More preferably Xaa<sub>1</sub> is His.

Preferred are those compounds wherein Xaa<sub>2</sub> is Gly.

Preferred are those compounds wherein Xaa<sub>3</sub> is Leu, pentylglycine or Met.

Preferred compounds include those wherein Xaa<sub>13</sub> is Trp or Phe.

Also preferred are compounds where Xaa<sub>4</sub> is Phe or naphthylalanine; Xaa<sub>11</sub> is Ile or Val and Xaa<sub>14</sub>, Xaa<sub>15</sub>, Xaa<sub>16</sub> and Xaa<sub>17</sub> are independently selected from Pro, homoproline, thioproline or N-alkylalanine. Preferably N-alkylalanine has a N-alkyl group of 1 to about 6 carbon atoms.

According to an especially preferred aspect, Xaa<sub>15</sub>, Xaa<sub>16</sub> and Xaa<sub>17</sub> are the same amino acid residue.

Preferred are compounds wherein Xaa<sub>18</sub> is Ser or Tyr, more preferably Ser.

Preferably Z is -NH<sub>2</sub>.

According to one aspect, preferred are compounds of

formula (I) wherein Xaa<sub>1</sub> is His or Tyr, more preferably His; Xaa<sub>2</sub> is Gly; Xaa<sub>4</sub> is Phe or naphthylalanine; Xaa<sub>9</sub> is Leu, pentylglycine or Met; Xaa<sub>10</sub> is Phe or naphthylalanine; Xaa<sub>11</sub> is Ile or Val; Xaa<sub>14</sub>, Xaa<sub>15</sub>, Xaa<sub>16</sub> and Xaa<sub>17</sub> are independently  
5 selected from Pro, homoproline, thioproline or N-alkylalanine; and Xaa<sub>18</sub> is Ser or Tyr, more preferably Ser. More preferably Z is -NH<sub>2</sub>.

According to an especially preferred aspect, especially preferred compounds include those of formula (I)  
10 wherein: Xaa<sub>1</sub> is His or Arg; Xaa<sub>2</sub> is Gly; Xaa<sub>3</sub> is Asp or Glu; Xaa<sub>4</sub> is Phe or naphthylalanine; Xaa<sub>5</sub> is Thr or Ser; Xaa<sub>6</sub> is Ser or Thr; Xaa<sub>7</sub> is Asp or Glu; Xaa<sub>8</sub> is Leu or pentylglycine; Xaa<sub>9</sub> is Leu or pentylglycine; Xaa<sub>10</sub> is Phe or naphthylalanine; Xaa<sub>11</sub> is Ile, Val or t-butyltylglycine;  
15 Xaa<sub>12</sub> is Glu or Asp; Xaa<sub>13</sub> is Trp or Phe; Xaa<sub>14</sub>, Xaa<sub>15</sub>, Xaa<sub>16</sub>, and Xaa<sub>17</sub> are independently Pro, homoproline, thioproline, or N-methylalanine; Xaa<sub>18</sub> is Ser or Tyr: and Z is -OH or -NH<sub>2</sub>; with the proviso that the compound does not have the formula of either SEQ. ID. NOS. 1 or 2. More preferably Z  
20 is -NH<sub>2</sub>. Especially preferred compounds include those having the amino acid sequence of SEQ. ID. NOS. 9, 10, 21, 22, 23, 26, 28, 34, 35 and 39.

According to an especially preferred aspect, provided  
25 are compounds where Xaa<sub>9</sub> is Leu, Ile, Val or pentylglycine,



more preferably Leu or pentylglycine, and Xaa<sub>13</sub> is Phe, Tyr or naphthylalanine, more preferably Phe or naphthylalanine. These compounds will exhibit advantageous duration of action and be less subject to oxidative degradation, both in vitro and in vivo, as well as during synthesis of the compound.

Exendin agonist compounds also include those described in U.S. Provisional Application No. 60/065,442, including compounds of the formula (II) [SEQ ID NO. 4]:

10

Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Gly Xaa<sub>5</sub> Xaa<sub>6</sub> Xaa<sub>7</sub> Xaa<sub>8</sub> Xaa<sub>9</sub> Xaa<sub>10</sub>  
Xaa<sub>11</sub> Xaa<sub>12</sub> Xaa<sub>13</sub> Xaa<sub>14</sub> Xaa<sub>15</sub> Xaa<sub>16</sub> Xaa<sub>17</sub> Ala Xaa<sub>19</sub> Xaa<sub>20</sub>  
Xaa<sub>21</sub> Xaa<sub>22</sub> Xaa<sub>23</sub> Xaa<sub>24</sub> Xaa<sub>25</sub> Xaa<sub>26</sub> Xaa<sub>27</sub> Xaa<sub>28</sub>-Z<sub>1</sub>; wherein

15

Xaa<sub>1</sub> is His, Arg or Tyr;  
Xaa<sub>2</sub> is Ser, Gly, Ala or Thr;  
Xaa<sub>3</sub> is Asp or Glu;  
Xaa<sub>5</sub> is Ala or Thr;  
Xaa<sub>6</sub> is Ala, Phe, Tyr or naphthylalanine;

20

Xaa<sub>7</sub> is Thr or Ser;  
Xaa<sub>8</sub> is Ala, Ser or Thr;  
Xaa<sub>9</sub> is Asp or Glu;  
Xaa<sub>10</sub> is Ala, Leu, Ile, Val, pentylglycine or Met;  
Xaa<sub>11</sub> is Ala or Ser;

25

Xaa<sub>12</sub> is Ala or Lys;

- Xaa<sub>13</sub> is Ala or Gln;  
 Xaa<sub>14</sub> is Ala, Leu, Ile, pentylglycine, Val or Met;  
 Xaa<sub>15</sub> is Ala or Glu;  
 Xaa<sub>16</sub> is Ala or Glu;  
 5 Xaa<sub>17</sub> is Ala or Glu;  
 Xaa<sub>19</sub> is Ala or Val;  
 Xaa<sub>20</sub> is Ala or Arg;  
 Xaa<sub>21</sub> is Ala or Leu;  
 Xaa<sub>22</sub> is Ala, Phe, Tyr or naphthylalanine;  
 10 Xaa<sub>23</sub> is Ile, Val, Leu, pentylglycine, tert-butylglycine  
 or Met;  
 Xaa<sub>24</sub> is Ala, Glu or Asp;  
 Xaa<sub>25</sub> is Ala, Trp, Phe, Tyr or naphthylalanine;  
 Xaa<sub>26</sub> is Ala or Leu;  
 15 Xaa<sub>27</sub> is Ala or Lys;  
 Xaa<sub>28</sub> is Ala or Asn;  
 Z<sub>1</sub> is-OH,  
 -NH<sub>2</sub>  
 Gly-Z<sub>2</sub>,  
 20 Gly Gly-Z<sub>2</sub>,  
 Gly Gly Xaa<sub>31</sub>-Z<sub>2</sub>,  
 Gly Gly Xaa<sub>31</sub> Ser-Z<sub>2</sub>,  
 Gly Gly Xaa<sub>31</sub> Ser Ser-Z<sub>2</sub>,  
 Gly Gly Xaa<sub>31</sub> Ser Ser Gly-Z<sub>2</sub>,  
 25 Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub>-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub> Xaa<sub>37</sub>-Z<sub>2</sub> or

Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub> Xaa<sub>37</sub> Xaa<sub>38</sub>-Z<sub>2</sub>;

Xaa<sub>31</sub>, Xaa<sub>36</sub>, Xaa<sub>37</sub> and Xaa<sub>38</sub> are independently Pro,

5 homoproline, 3Hyp, 4Hyp, thioproline,

N-alkylglycine, N-alkylpentylglycine or

N-alkylalanine; and

Z<sub>2</sub> is -OH or -NH<sub>2</sub>;

provided that no more than three of Xaa<sub>3</sub>, Xaa<sub>5</sub>, Xaa<sub>6</sub>, Xaa<sub>8</sub>,

10 Xaa<sub>10</sub>, Xaa<sub>11</sub>, Xaa<sub>12</sub>, Xaa<sub>13</sub>, Xaa<sub>14</sub>, Xaa<sub>15</sub>, Xaa<sub>16</sub>, Xaa<sub>17</sub>, Xaa<sub>19</sub>,

Xaa<sub>20</sub>, Xaa<sub>21</sub>, Xaa<sub>24</sub>, Xaa<sub>25</sub>, Xaa<sub>26</sub>, Xaa<sub>27</sub> and Xaa<sub>28</sub> are Ala.

Preferred N-alkyl groups for N-alkylglycine, N-

alkylpentylglycine and N-alkylalanine include lower alkyl

groups preferably of 1 to about 6 carbon atoms, more

15 preferably of 1 to 4 carbon atoms.

Preferred exendin agonist compounds include those

wherein Xaa<sub>1</sub> is His or Tyr. More preferably Xaa<sub>1</sub> is His.

Preferred are those compounds wherein Xaa<sub>2</sub> is Gly.

Preferred are those compounds wherein Xaa<sub>14</sub> is Leu,

20 pentylglycine or Met.

Preferred compounds are those wherein Xaa<sub>25</sub> is Trp or  
Phe.

Preferred compounds are those where Xaa<sub>6</sub> is Phe or  
naphthylalanine; Xaa<sub>22</sub> is Phe or naphthylalanine and

25 Xaa<sub>23</sub> is Ile or Val.

Preferred are compounds wherein Xaa<sub>31</sub>, Xaa<sub>36</sub>, Xaa<sub>37</sub> and Xaa<sub>38</sub> are independently selected from Pro, homoproline, thioproline and N-alkylalanine.

Preferably Z<sub>1</sub> is -NH<sub>2</sub>.

5           Preferable Z<sub>2</sub> is -NH<sub>2</sub>.

According to one aspect, preferred are compounds of formula (I) wherein Xaa<sub>1</sub> is His or Tyr, more preferably His; Xaa<sub>2</sub> is Gly; Xaa<sub>6</sub> is Phe or naphthylalanine; Xaa<sub>14</sub> is Leu, pentylglycine or Met; Xaa<sub>22</sub> is Phe or naphthylalanine; Xaa<sub>23</sub>  
10           is Ile or Val; Xaa<sub>31</sub>, Xaa<sub>36</sub>, Xaa<sub>37</sub> and Xaa<sub>38</sub> are independently selected from Pro, homoproline, thioproline or N-alkylalanine. More preferably Z<sub>1</sub> is -NH<sub>2</sub>.

According to an especially preferred aspect, especially preferred compounds include those of formula (I)  
15           wherein: Xaa<sub>1</sub> is His or Arg; Xaa<sub>2</sub> is Gly or Ala; Xaa<sub>3</sub> is Asp or Glu; Xaa<sub>5</sub> is Ala or Thr; Xaa<sub>6</sub> is Ala, Phe or naphthylalanine; Xaa<sub>7</sub> is Thr or Ser; Xaa<sub>8</sub> is Ala, Ser or Thr; Xaa<sub>9</sub> is Asp or Glu; Xaa<sub>10</sub> is Ala, Leu or pentylglycine; Xaa<sub>11</sub> is Ala or Ser; Xaa<sub>12</sub> is Ala or Lys; Xaa<sub>13</sub> is Ala or Gln; Xaa<sub>14</sub>  
20           is Ala, Leu or pentylglycine; Xaa<sub>15</sub> is Ala or Glu; Xaa<sub>16</sub> is Ala or Glu; Xaa<sub>17</sub> is Ala or Glu; Xaa<sub>19</sub> is Ala or Val; Xaa<sub>20</sub> is Ala or Arg; Xaa<sub>21</sub> is Ala or Leu; Xaa<sub>22</sub> is Phe or naphthylalanine; Xaa<sub>23</sub> is Ile, Val or tert-butylglycine; Xaa<sub>24</sub> is Ala, Glu or Asp; Xaa<sub>25</sub> is Ala, Trp or Phe; Xaa<sub>26</sub> is  
25           Ala or Leu; Xaa<sub>27</sub> is Ala or Lys; Xaa<sub>28</sub> is Ala or Asn; Z<sub>1</sub> is -

OH, -NH<sub>2</sub>, Gly-Z<sub>2</sub>, Gly Gly-Z<sub>2</sub>, Gly Gly Xaa<sub>31</sub>-Z<sub>2</sub>, Gly Gly Xaa<sub>31</sub>  
 Ser-Z<sub>2</sub>, Gly Gly Xaa<sub>31</sub> Ser Ser-Z<sub>2</sub>, Gly Gly Xaa<sub>31</sub> Ser Ser Gly-  
 Z<sub>2</sub>, Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala-Z<sub>2</sub>, Gly Gly Xaa<sub>31</sub> Ser Ser  
 Gly Ala Xaa<sub>36</sub>-Z<sub>2</sub>, Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub> Xaa<sub>37</sub>-Z<sub>2</sub>,  
 5 Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub> Xaa<sub>37</sub> Xaa<sub>38</sub>-Z<sub>2</sub>; Xaa<sub>31</sub>, Xaa<sub>36</sub>,  
 Xaa<sub>37</sub> and Xaa<sub>38</sub> being independently Pro homoproline,  
 thioproline or N-methylalanine; and Z<sub>2</sub> being -OH or -NH<sub>2</sub>;  
 provided that no more than three of Xaa<sub>3</sub>, Xaa<sub>5</sub>, Xaa<sub>6</sub>, Xaa<sub>8</sub>,  
 Xaa<sub>10</sub>, Xaa<sub>11</sub>, Xaa<sub>12</sub>, Xaa<sub>13</sub>, Xaa<sub>14</sub>, Xaa<sub>15</sub>, Xaa<sub>16</sub>, Xaa<sub>17</sub>, Xaa<sub>19</sub>,  
 10 Xaa<sub>20</sub>, Xaa<sub>21</sub>, Xaa<sub>24</sub>, Xaa<sub>25</sub>, Xaa<sub>26</sub>, Xaa<sub>27</sub> and Xaa<sub>28</sub> are Ala.  
 Especially preferred compounds include those having the  
 amino acid sequence of SEQ. ID. NOS. 40-61.

According to an especially preferred aspect, provided  
 are compounds where Xaa<sub>14</sub> is Leu, Ile, Val or pentylglycine,  
 15 more preferably Leu or pentylglycine, and Xaa<sub>25</sub> is Phe, Tyr  
 or naphthylalanine, more preferably Phe or naphthylalanine.  
 These compounds will be less susceptible to oxidative  
 degradation, both in vitro and in vivo, as well as during  
 synthesis of the compound.

20 Exendin agonist compounds also include those described  
 in U.S. Provisional Application No. 60/066,029, including  
 compounds of the formula (III)[SEQ ID NO. 5]:

Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Xaa<sub>4</sub> Xaa<sub>5</sub> Xaa<sub>6</sub> Xaa<sub>7</sub> Xaa<sub>8</sub> Xaa<sub>9</sub> Xaa<sub>10</sub>  
 25 Xaa<sub>11</sub> Xaa<sub>12</sub> Xaa<sub>13</sub> Xaa<sub>14</sub> Xaa<sub>15</sub> Xaa<sub>16</sub> Xaa<sub>17</sub> Ala Xaa<sub>19</sub> Xaa<sub>20</sub>

Xaa<sub>21</sub> Xaa<sub>22</sub> Xaa<sub>23</sub> Xaa<sub>24</sub> Xaa<sub>25</sub> Xaa<sub>26</sub> Xaa<sub>27</sub> Xaa<sub>28</sub>-Z<sub>1</sub>; wherein

Xaa<sub>1</sub> is His, Arg, Tyr, Ala, Norval, Val  
or Norleu;

5 Xaa<sub>2</sub> is Ser, Gly, Ala or Thr;

Xaa<sub>3</sub> is Ala, Asp or Glu;

Xaa<sub>4</sub> is Ala, Norval, Val, Norleu or Gly;

Xaa<sub>5</sub> is Ala or Thr;

Xaa<sub>6</sub> is Phe, Tyr or naphthylalanine;

10 Xaa<sub>7</sub> is Thr or Ser;

Xaa<sub>8</sub> is Ala, Ser or Thr;

Xaa<sub>9</sub> is Ala, Norval, Val, Norleu, Asp or Glu;

Xaa<sub>10</sub> is Ala, Leu, Ile, Val, pentylglycine or Met;

Xaa<sub>11</sub> is Ala or Ser;

15 Xaa<sub>12</sub> is Ala or Lys;

Xaa<sub>13</sub> is Ala or Gln;

Xaa<sub>14</sub> is Ala, Leu, Ile, pentylglycine, Val or Met;

Xaa<sub>15</sub> is Ala or Glu;

Xaa<sub>16</sub> is Ala or Glu;

20 Xaa<sub>17</sub> is Ala or Glu;

Xaa<sub>19</sub> is Ala or Val;

Xaa<sub>20</sub> is Ala or Arg;

Xaa<sub>21</sub> is Ala or Leu;

Xaa<sub>22</sub> is Phe, Tyr or naphthylalanine;

25 Xaa<sub>23</sub> is Ile, Val, Leu, pentylglycine, tert-butylglycine or

Met;

Xaa<sub>24</sub> is Ala, Glu or Asp;

Xaa<sub>25</sub> is Ala, Trp, Phe, Tyr or naphthylalanine;

Xaa<sub>26</sub> is Ala or Leu;

5 Xaa<sub>27</sub> is Ala or Lys;

Xaa<sub>28</sub> is Ala or Asn;

Z<sub>1</sub> is -OH,

-NH<sub>2</sub>,

Gly-Z<sub>2</sub>,

10 Gly Gly-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub>-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser Ser-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser Ser Gly-Z<sub>2</sub>,

15 Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub>-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub> Xaa<sub>37</sub>-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub> Xaa<sub>37</sub> Xaa<sub>38</sub>-Z<sub>2</sub> or Gly

Gly Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub> Xaa<sub>37</sub> Xaa<sub>38</sub> Xaa<sub>39</sub>-Z<sub>2</sub>; wherein

20 Xaa<sub>31</sub>, Xaa<sub>36</sub>, Xaa<sub>37</sub> and Xaa<sub>38</sub> are independently

Pro, homoproline, 3Hyp, 4Hyp, thioproline,

N-alkylglycine, N-alkylpentylglycine or

N-alkylalanine; and

Z<sub>2</sub> is -OH or -NH<sub>2</sub>;

25 provided that no more than three of Xaa<sub>3</sub>, Xaa<sub>4</sub>, Xaa<sub>5</sub>, Xaa<sub>6</sub>,

Xaa<sub>8</sub>, Xaa<sub>9</sub>, Xaa<sub>10</sub>, Xaa<sub>11</sub>, Xaa<sub>12</sub>, Xaa<sub>13</sub>, Xaa<sub>14</sub>, Xaa<sub>15</sub>, Xaa<sub>16</sub>, Xaa<sub>17</sub>,  
Xaa<sub>19</sub>, Xaa<sub>20</sub>, Xaa<sub>21</sub>, Xaa<sub>24</sub>, Xaa<sub>25</sub>, Xaa<sub>26</sub>, Xaa<sub>27</sub> and Xaa<sub>28</sub> are  
Ala; and provided also that, if Xaa<sub>1</sub> is His, Arg or Tyr,  
then at least one of Xaa<sub>3</sub>, Xaa<sub>4</sub> and Xaa<sub>9</sub> is Ala.

5

### Definitions

In accordance with the present invention and as used  
herein, the following terms are defined to have the  
following meanings, unless explicitly stated otherwise.

- 10       The term "amino acid" refers to natural amino acids,  
unnatural amino acids, and amino acid analogs, all in their  
D and L stereoisomers if their structure allow such  
stereoisomeric forms. Natural amino acids include alanine  
(Ala), arginine (Arg), asparagine (Asn), aspartic acid  
15       (Asp), cysteine (Cys), glutamine (Gln), glutamic acid  
(Glu), glycine (Gly), histidine (His), isoleucine (Ile),  
leucine (Leu), Lysine (Lys), methionine (Met),  
phenylalanine (Phe), proline (Pro), serine (Ser), threonine  
(Thr), typtophan (Trp), tyrosine (Tyr) and valine (Val).
- 20       Unnatural amino acids include, but are not limited to  
azetidinecarboxylic acid, 2-aminoadipic acid, 3-aminoadipic  
acid, beta-alanine, aminopropionic acid, 2-aminobutyric  
acid, 4-aminobutyric acid, 6-aminocaproic acid, 2-  
aminoheptanoic acid, 2-aminoisobutyric acid, 3-  
25       aminoisbutyric acid, 2-aminopimelic acid, tertiary-

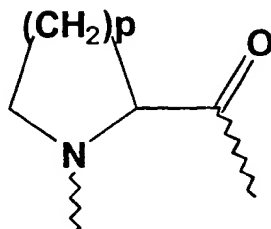


butylglycine, 2,4-diaminoisobutyric acid, desmosine, 2,2'-  
diaminopimelic acid, 2,3-diaminopropionic acid, N-  
ethylglycine, N-ethylasparagine, homoproline,  
hydroxylysine, allo-hydroxylysine, 3-hydroxyproline, 4-  
5 hydroxyproline, isodesmosine, allo-isoleucine, N-  
methylalanine, N-methylglycine, N-methylisoleucine, N-  
methylpentylglycine, N-methylvaline, naphthalanine,  
norvaline, norleucine, ornithine, pentylglycine, pipecolic  
acid and thioproline. Amino acid analogs include the  
10 natural and unnatural amino acids which are chemically  
blocked, reversibly or irreversibly, or modified on their  
N-terminal amino group or their side-chain groups, as for  
example, methionine sulfoxide, methionine sulfone, S-  
(carboxymethyl)-cysteine, S-(carboxymethyl)-cysteine  
15 sulfoxide and S-(carboxymethyl)-cysteine sulfone.

The term "amino acid analog" refers to an amino acid  
wherein either the C-terminal carboxy group, the N-terminal  
amino group or side-chain functional group has been  
chemically codified to another functional group. For  
20 example, aspartic acid-(beta-methyl ester) is an amino acid  
analog of aspartic acid; N-ethylglycine is an amino acid  
analog of glycine; or alanine carboxamide is an amino acid  
analog of alanine.

The term "amino acid residue" refers to radicals  
25 having the structure: (1)  $-C(O)-R-NH-$ , wherein R typically

is  $-\text{CH}(\text{R}')-$ , wherein  $\text{R}'$  is an amino acid side chain, typically H or a carbon containing substituent; or (2),



5

wherein  $p$  is 1, 2 or 3 representing the azetidinecarboxylic acid, proline or pipercolic acid residues, respectively.

The term "lower" referred to herein in connection with organic radicals such as alkyl groups defines such groups with up to and including about 6, preferably up to and including 4 and advantageously one or two carbon atoms. Such groups may be straight chain or branched chain.

"Pharmaceutically acceptable salt" includes salts of the compounds described herein derived from the combination of such compounds and an organic or inorganic acid. In practice the use of the salt form amounts to use of the base form. The compounds are useful in both free base and salt form.

In addition, the following abbreviations stand for the following:

"ACN" or " $\text{CH}_3\text{CN}$ " refers to acetonitrile.

"Boc", "tBoc" or "Tboc" refers to t-butoxy carbonyl.

"DCC" refers to N,N'-dicyclohexylcarbodiimide.

"Fmoc" refers to fluorenylmethoxycarbonyl.

"HBTU" refers to 2-(1H-benzotriazol-1-yl)-  
1,1,3,3,-tetramethyluronium hexafluorophosphate.

5 "HOBt" refers to 1-hydroxybenzotriazole monohydrate.

"homoP" or hPro" refers to homoproline.

"MeAla" or "Nme" refers to N-methylalanine.

"naph" refers to naphthylalanine.

"pG" or pGly" refers to pentylglycine.

10 "tBuG" refers to tertiary-butylglycine.

"ThioP" or tPro" refers to thioproline.

3Hyp" refers to 3-hydroxyproline

4Hyp" refers to 4-hydroxyproline

NAG" refers to N-alkylglycine

15 NAPG" refers to N-alkylpentylglycine

"Norval" refers to norvaline

"Norleu" refers to norleucine

## 20 Preparation of Compounds

The exendins and exendin agonists described herein may be prepared using standard solid-phase peptide synthesis techniques and preferably an automated or semiautomated peptide synthesizer. Typically, using such techniques, an

25  $\alpha$ -N-carbamoyl protected amino acid and an amino acid

attached to the growing peptide chain on a resin are coupled at room temperature in an inert solvent such as dimethylformamide, N-methylpyrrolidinone or methylene chloride in the presence of coupling agents such as  
5 dicyclohexylcarbodiimide and 1-hydroxybenzotriazole in the presence of a base such as diisopropylethylamine. The  $\alpha$ -N-carbamoyl protecting group is removed from the resulting peptide-resin using a reagent such as trifluoroacetic acid or piperidine, and the coupling reaction repeated with the  
10 next desired N-protected amino acid to be added to the peptide chain. Suitable N-protecting groups are well known in the art, with t-butyloxycarbonyl (tBoc) and fluorenylmethoxycarbonyl (Fmoc) being preferred herein.

The solvents, amino acid derivatives and  
15 4-methylbenzhydryl-amine resin used in the peptide synthesizer may be purchased from Applied Biosystems Inc. (Foster City, CA). The following side-chain protected amino acids may be purchased from Applied Biosystems, Inc.:  
Boc-Arg(Mts), Fmoc-Arg(Pmc), Boc-Thr(Bzl), Fmoc-Thr(t-Bu),  
20 Boc-Ser(Bzl), Fmoc-Ser(t-Bu), Boc-Tyr(BrZ), Fmoc-Tyr(t-Bu), Boc-Lys(Cl-Z), Fmoc-Lys(Boc), Boc-Glu(Bzl), Fmoc-Glu(t-Bu), Fmoc-His(Trt), Fmoc-Asn(Trt), and Fmoc-Gln(Trt).

Boc-His(BOM) may be purchased from Applied Biosystems, Inc. or Bachem Inc. (Torrance, CA). Anisole, dimethylsulfide,  
25 phenol, ethanedithiol, and thioanisole may be obtained from

Aldrich Chemical Company (Milwaukee, WI). Air Products and Chemicals (Allentown, PA) supplies HF. Ethyl ether, acetic acid and methanol may be purchased from Fisher Scientific (Pittsburgh, PA).

5           Solid phase peptide synthesis may be carried out with an automatic peptide synthesizer (Model 430A, Applied Biosystems Inc., Foster City, CA) using the NMP/HOBt (Option 1) system and tBoc or Fmoc chemistry (see, Applied Biosystems User's Manual for the ABI 430A Peptide  
10           Synthesizer, Version 1.3B July 1, 1988, section 6, pp. 49-70, Applied Biosystems, Inc., Foster City, CA) with capping. Boc-peptide-resins may be cleaved with HF (-5° C to 0° C, 1 hour). The peptide may be extracted from the resin with alternating water and acetic acid, and the  
15           filtrates lyophilized. The Fmoc-peptide resins may be cleaved according to standard methods (Introduction to Cleavage Techniques, Applied Biosystems, Inc., 1990, pp. 6-12). Peptides may be also be assembled using an Advanced Chem Tech Synthesizer (Model MPS 350, Louisville,  
20           Kentucky).

          Peptides may be purified by RP-HPLC (preparative and analytical) using a Waters Delta Prep 3000 system. A C4, C8 or C18 preparative column (10 $\mu$  , 2.2 x 25 cm; Vydac, Hesperia, CA) may be used to isolate peptides, and purity  
25           may be determined using a C4, C8 or C18 analytical column

(5 $\mu$  , 0.46 x 25 cm; Vydac). Solvents (A=0.1% TFA/water and B=0.1% TFA/CH<sub>3</sub>CN) may be delivered to the analytical column at a flowrate of 1.0 ml/min and to the preparative column at 15 ml/min. Amino acid analyses may be performed on the  
5 Waters Pico Tag system and processed using the Maxima program. Peptides may be hydrolyzed by vapor-phase acid hydrolysis (115° C, 20-24 h). Hydrolysates may be derivatized and analyzed by standard methods (Cohen, et al., The Pico Tag Method: A Manual of Advanced Techniques  
10 for Amino Acid Analysis, pp. 11-52, Millipore Corporation, Milford, MA (1989)). Fast atom bombardment analysis may be carried out by M-Scan, Incorporated (West Chester, PA). Mass calibration may be performed using cesium iodide or cesium iodide/glycerol. Plasma desorption ionization  
15 analysis using time of flight detection may be carried out on an Applied Biosystems Bio-Ion 20 mass spectrometer. Electrospray mass spectroscopy may be carried out on a VG-Trio machine.

Peptide compounds useful in the invention may also  
20 be prepared using recombinant DNA techniques, using methods now known in the art. See, e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual, 2d Ed., Cold Spring Harbor (1989). Non-peptide compounds useful in the present invention may be prepared by art-known methods. For  
25 example, phosphate-containing amino acids and peptides

containing such amino acids, may be prepared using methods known in the art. See, e.g., Bartlett and Landen, Biorg. Chem. 14:356-377 (1986).

5 The compounds described above are useful in view of their pharmacological properties. In particular, the compounds of the invention possess activity as agents to reduce food intake. They can be used to treat conditions or diseases which can be alleviated by reducing food intake.

10 Compositions useful in the invention may conveniently be provided in the form of formulations suitable for parenteral (including intravenous, intramuscular and subcutaneous) or nasal or oral administration. In some cases, it will be convenient to provide an exendin or exendin agonist and another food-intake-reducing, plasma  
15 glucose-lowering or plasma lipid-lowering agent, such as amylin, an amylin agonist, a CCK, or a leptin, in a single composition or solution for administration together. In other cases, it may be more advantageous to administer the additional agent separately from said exendin or exendin  
20 agonist. A suitable administration format may best be determined by a medical practitioner for each patient individually. Suitable pharmaceutically acceptable carriers and their formulation are described in standard formulation treatises, e.g., Remington's Pharmaceutical Sciences by E.W.  
25 Martin. See also Wang, Y.J. and Hanson, M.A. "Parenteral

Formulations of Proteins and Peptides: Stability and Stabilizers," Journal of Parenteral Science and Technology, Technical Report No. 10, Supp. 42:2S (1988).

Compounds useful in the invention can be provided as parenteral compositions for injection or infusion. They can, for example, be suspended in an inert oil, suitably a vegetable oil such as sesame, peanut, olive oil, or other acceptable carrier. Preferably, they are suspended in an aqueous carrier, for example, in an isotonic buffer solution at a pH of about 3.0 to 8.0, preferably at a pH of about 3.5 to 5.0. These compositions may be sterilized by conventional sterilization techniques, or may be sterile filtered. The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions, such as pH buffering agents. Useful buffers include for example, sodium acetate/acetic acid buffers. A form of repository or "depot" slow release preparation may be used so that therapeutically effective amounts of the preparation are delivered into the bloodstream over many hours or days following transdermal injection or delivery.

The desired isotonicity may be accomplished using sodium chloride or other pharmaceutically acceptable agents such as dextrose, boric acid, sodium tartrate, propylene glycol, polyols (such as mannitol and sorbitol), or other



inorganic or organic solutes. Sodium chloride is preferred particularly for buffers containing sodium ions.

The claimed compositions can also be formulated as pharmaceutically acceptable salts (e.g., acid addition salts) and/or complexes thereof. Pharmaceutically acceptable salts are non-toxic salts at the concentration at which they are administered. The preparation of such salts can facilitate the pharmacological use by altering the physical-chemical characteristics of the composition without preventing the composition from exerting its physiological effect. Examples of useful alterations in physical properties include lowering the melting point to facilitate transmucosal administration and increasing the solubility to facilitate the administration of higher concentrations of the drug.

Pharmaceutically acceptable salts include acid addition salts such as those containing sulfate, hydrochloride, phosphate, sulfamate, acetate, citrate, lactate, tartrate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, cyclohexylsulfamate and quinate. Pharmaceutically acceptable salts can be obtained from acids such as hydrochloric acid, sulfuric acid, phosphoric acid, sulfamic acid, acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic

acid, cyclohexylsulfamic acid, and quinic acid. Such salts may be prepared by, for example, reacting the free acid or base forms of the product with one or more equivalents of the appropriate base or acid in a solvent or medium in which  
5 the salt is insoluble, or in a solvent such as water which is then removed in vacuo or by freeze-drying or by exchanging the ions of an existing salt for another ion on a suitable ion exchange resin.

Carriers or excipients can also be used to facilitate  
10 administration of the compound. Examples of carriers and excipients include calcium carbonate, calcium phosphate, various sugars such as lactose, glucose, or sucrose, or types of starch, cellulose derivatives, gelatin, vegetable oils, polyethylene glycols and physiologically compatible  
15 solvents. The compositions or pharmaceutical composition can be administered by different routes including intravenously, intraperitoneal, subcutaneous, and intramuscular, orally, topically, transmucosally, or by pulmonary inhalation.

20 If desired, solutions of the above compositions may be thickened with a thickening agent such as methyl cellulose.

They may be prepared in emulsified form, either water in oil or oil in water. Any of a wide variety of pharmaceutically acceptable emulsifying agents may be  
25 employed including, for example, acacia powder, a non-ionic

surfactant (such as a Tween), or an ionic surfactant (such as alkali polyether alcohol sulfates or sulfonates, e.g., a Triton).

5 Compositions useful in the invention are prepared by mixing the ingredients following generally accepted procedures. For example, the selected components may be simply mixed in a blender or other standard device to produce a concentrated mixture which may then be adjusted to the final concentration and viscosity by the addition of  
10 water or thickening agent and possibly a buffer to control pH or an additional solute to control tonicity.

For use by the physician, the compositions will be provided in dosage unit form containing an amount of an exendin or exendin agonist, for example, exendin-3, and/or  
15 exendin-4, with or without another food intake-reducing, plasma glucose-lowering or plasma lipid-lowering agent. Therapeutically effective amounts of an exendin or exendin agonist for use in reducing food intake are those that suppress appetite at a desired level. As will be recognized  
20 by those in the field, an effective amount of therapeutic agent will vary with many factors including the age and weight of the patient, the patient's physical condition, the blood sugar level and other factors.

The effective daily appetite-suppressing dose of the  
25 compounds will typically be in the range of about 10 to 30

$\mu\text{g}$  to about 5 mg/day, preferably about 10 to 30  $\mu\text{g}$  to about 2 mg/day and more preferably about 10 to 100  $\mu\text{g}$  to about 1 mg/day, most preferably about 30  $\mu\text{g}$  to about 500  $\mu\text{g}$ /day, for a 70 kg patient, administered in a single or divided doses.

5     The exact dose to be administered is determined by the attending clinician and is dependent upon where the particular compound lies within the above quoted range, as well as upon the age, weight and condition of the individual. Administration should begin whenever the  
10    suppression of food intake, or weight lowering is desired, for example, at the first sign of symptoms or shortly after diagnosis of obesity, diabetes mellitus, or insulin-resistance syndrome. Administration may be by injection, preferably subcutaneous or intramuscular. Orally active  
15    compounds may be taken orally, however dosages should be increased 5-10 fold.

      The optimal formulation and mode of administration of compounds of the present application to a patient depend on factors known in the art such as the particular disease or  
20    disorder, the desired effect, and the type of patient. While the compounds will typically be used to treat human subjects they may also be used to treat similar or identical diseases in other vertebrates such as other primates, farm animals such as swine, cattle and poultry, and sports  
25    animals and pets such as horses, dogs and cats.

To assist in understanding the present invention, the following Examples are included. The experiments relating to this invention should not, of course, be construed as specifically limiting the invention and such variations of the invention, now known or later developed, which would be within the purview of one skilled in the art are considered to fall within the scope of the invention as described herein and hereinafter claimed.

EXAMPLE 1: Exendin Injections Reduced the Food Intake of  
Normal Mice

All mice (NIH:Swiss mice) were housed in a stable environment of 22 ( $\pm$  2) $^{\circ}$  C, 60 ( $\pm$ 10) % humidity and a 12:12 light:dark cycle; with lights on at 0600. Mice were housed in groups of four in standard cages with *ad libitum* access to food (Teklad: LM 485; Madison, WI) and water except as noted, for at least two weeks before the experiments.

All experiments were conducted between the hours of 0700 and 0900. The mice were food deprived (food removed at 1600 hr from all animals on day prior to experiment) and individually housed. All mice received an intraperitoneal injection (5  $\mu$ l/kg) of either saline or exendin-4 at doses of 0.1, 1.0, 10 and 100  $\mu$ g/kg and were immediately presented with a pre-weighed food pellet (Teklad LM 485). The food pellet was weighed at 30-minute, 1-hr, 2-hr and 6-hr

intervals to determine the amount of food eaten.

Figure 1 depicts cumulative food intake over periods of 0.5, 1, 2 and 6hr in overnight-fasted normal NIH:Swiss mice following ip injection of saline, 2 doses of GLP-1, or 4  
5 doses of exendin-4. At doses up to 100µg/kg, GLP-1 had no effect on food intake measured over any period, a result consistent with that previously reported (Bhavsar, S.P., et al., Soc. Neurosci. Abstr. 21:460 (188.8) (1995); and Turton, M.D., Nature, 379:69-72, (1996)).

10 In contrast, exendin-4 injections potently and dose-dependently inhibited food intake. The ED<sub>50</sub> for inhibition of food intake over 30 min was 1µg/kg, which is a level about as potent as amylin (ED<sub>50</sub> 3.6µg/kg) or the prototypical peripheral satiety agent, CCK (ED<sub>50</sub> 0.97µg/kg) as measured in  
15 this preparation. However, in contrast to the effects of amylin or CCK, which abate after 1-2 hours, the inhibition of food intake with exendin-4 was still present after at least 6 hours after injection.

20 EXAMPLE 2: Exendin Reduced the Food Intake of Obese Mice

All mice (female ob/ob mice) were housed in a stable environment of 22 (±2)° C, 60 (±10) % humidity and a 12:12 light:dark cycle; with lights on at 0600. Mice were housed in groups of four in standard cages with *ad libitum* access  
25 to food (Teklad: LM 485) and water except as noted, for at

least two weeks before the experiments.

All experiments were conducted between the hours of 0700 and 0900. The mice were food deprived (food removed at 1600 hr from all animals on day prior to experiment) and individually housed. All mice received an intraperitoneal injection (5  $\mu$ l/kg) of either saline or exendin-4 at doses of 0.1, 1.0 and 10  $\mu$ g/kg (female ob/ob mice) and were immediately presented with a pre-weighed food pellet (Teklad LM 485). The food pellet was weighed at 30-minute, 1 -hr, 2-hr and 6-hr intervals to determine the amount of food eaten.

Figure 2 depicts the effect of exendin-4 in the ob/ob mouse model of obesity. The obese mice had a similar food intake-related response to exendin as the normal mice. Moreover, the obese mice were not hypersensitive to exendin, as has been observed with amylin and leptin (Young, A.A., et al., Program and Abstracts, 10th International Congress of Endocrinology, June 12-15, 1996 San Francisco, pg 419 (P2-58)).

### EXAMPLE 3: Intracerebroventricular Injections of Exendin

#### Inhibited Food Intake in Rats

All rats (Harlan Sprague-Dawley) were housed in a stable environment of 22 ( $\pm$ 2) $^{\circ}$  C, 60 ( $\pm$ 10)% humidity and a 12:12 light:dark cycle; with lights on at 0600. Rats were

obtained from Zivic Miller with an intracerebroventricular cannula (ICV cannula) implanted (coordinates determined by actual weight of animals and referenced to Paxinos, G. and Watson, C. "The Rat Brain in stereotaxic coordinates," second edition. Academic Press) and were individually housed in standard cages with *ad libitum* access to food (Teklad: LM 485) and water for at least one week before the experiments.

All injections were given between the hours of 1700 and 1800. The rats were habituated to the ICV injection procedure at least once before the ICV administration of compound. All rats received an ICV injection (2  $\mu$ l/30 seconds) of either saline or exendin-4 at doses of 0.01, 0.03, 0.1, 0.3, and 1.0  $\mu$ g. All animals were then presented with pre-weighed food (Teklad LM 485) at 1800, when the lights were turned off. The amount of food left was weighed at 2-hr, 12-hr and 24-hr intervals to determine the amount of food eaten by each animal.

Figure 3 depicts a dose-dependent inhibition of food intake in rats that received doses greater than 0.1 $\mu$ g/rat. The ED<sub>50</sub> was  $\approx$  0.1 $\mu$ g, exendin-4 is thus  $\approx$ 100-fold more potent than intracerebroventricular injections of GLP-1 as reported by Turton, M.D., et al. (Nature 379:69-72 (1996)).

EXAMPLE 4: Exendin Agonists Reduced the Food Intake in



Mice

All mice (NIH:Swiss mice) were housed in a stable environment of 22 ( $\pm 2$ )° C, 60 ( $\pm 10$ ) % humidity and a 12:12 light:dark cycle; with lights on at 0600. Mice were housed  
5 in groups of four in standard cages with *ad libitum* access to food (Teklad: LM 485; Madison, WI) and water except as noted, for at least two weeks before the experiments.

All experiments were conducted between the hours of 0700 and 0900. The mice were food deprived (food removed  
10 at 1600 hr from all animals on day prior to experiment) and individually housed. All mice received an intraperitoneal injection (5  $\mu$ l/kg) of either saline or test compound at doses of 1, 10, and 100  $\mu$ g/kg and immediately presented  
15 with a food pellet (Teklad LM 485). The food pellet was weighed at 30-minute, 1-hr, 2-hr and 6-hr intervals to determine the amount of food eaten.

Figure 4 depicts the cumulative food intake over periods of 0.5, 1, 2 and 6 hr in overnight-fasted normal NIH:Swiss mice following ip injection of saline or exendin-  
20 4 (1-30) ("Compound 1") in doses of 1, 10 and 100  $\mu$ g/kg.

Figure 5 depicts the cumulative food intake over periods of 0.5, 1, 2 and 6 hr in overnight-fasted normal NIH:Swiss mice following ip injection of saline or exendin-  
25  $\mu$ g/kg. 4 (1-30) amide ("Compound 2") in doses of 1, 10 and 100  $\mu$ g/kg.

Figure 6 depicts the cumulative food intake over periods of 0.5, 1, 2 and 6 hr in overnight-fasted normal NIH:Swiss mice following ip injection of saline or exendin-4 (1-28) amide ("Compound 3") in doses of 1, 10 and 100  $\mu\text{g/kg}$ .

Figure 7 depicts the cumulative food intake over periods of 0.5, 1, 2 and 6 hr in overnight-fasted normal NIH:Swiss mice following ip injection of saline or  $^{14}\text{Leu}$ ,  $^{25}\text{Phe}$  exendin-4 amide ("Compound 4") in doses of 1, 10 and 100  $\mu\text{g/kg}$ .

Figure 8 depicts the cumulative food intake over periods of 0.5, 1, 2 and 6 hr in overnight-fasted normal NIH:Swiss mice following ip injection of saline or  $^{14}\text{Leu}$ ,  $^{25}\text{Phe}$  exendin-4 (1-28) amide ("Compound 5") in doses of 1, 10 and 100  $\mu\text{g/kg}$ .

Figure 9 depicts the cumulative food intake over periods of 0.5, 1, 2 and 6 hr in overnight-fasted normal NIH:Swiss mice following ip injection of saline or  $^{14}\text{Leu}$ ,  $^{22}\text{Ala}$ ,  $^{25}\text{Phe}$  exendin-4 (1-28) amide ("Compound 6") in doses of 1, 10 and 100  $\mu\text{g/kg}$ .

#### EXAMPLE 5

##### Preparation of amidated peptide having SEQ. ID. NO. 9

The above-identified peptide was assembled on 4-(2'-

4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.). In  
general, single-coupling cycles were used throughout the  
5 synthesis and Fast Moc (HBTU activation) chemistry was  
employed. However, at some positions coupling was less  
efficient than expected and double couplings were required.  
In particular, residues Asp<sub>9</sub>, Thr, and Phe<sub>6</sub> all required  
double coupling. Deprotection (Fmoc group removal) of the  
10 growing peptide chain using piperidine was not always  
efficient. Double deprotection was required at positions  
Arg<sub>20</sub>, Val<sub>19</sub>, and Leu<sub>14</sub>. Final deprotection of the completed  
peptide resin was achieved using a mixture of  
triethylsilane (0.2 mL), ethanedithiol (0.2 mL), anisole  
15 (0.2 mL), water (0.2 mL) and trifluoroacetic acid (15 mL)  
according to standard methods (Introduction to Cleavage  
Techniques, Applied Biosystems, Inc.) The peptide was  
precipitated in ether/water (50 mL) and centrifuged. The  
precipitate was reconstituted in glacial acetic acid and  
20 lyophilized. The lyophilized peptide was dissolved in  
water). Crude purity was about 55%.

Used in purification steps and analysis were Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).

The solution containing peptide was applied to a  
25 preparative C-18 column and purified (10% to 40% Solvent B

in Solvent A over 40 minutes). Purity of fractions was determined isocratically using a C-18 analytical column. Pure fractions were pooled furnishing the above-identified peptide. Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 14.5 minutes. Electrospray Mass Spectrometry (M): calculated 4131.7; found 4129.3.

10

EXAMPLE 6Preparation of Peptide having SEQ. ID. NO. 10

The above-identified peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 5. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 25% to 75% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 21.5 minutes. Electrospray Mass Spectrometry (M): calculated 4168.6; found 4171.2.

25

EXAMPLE 7Preparation of Peptide having SEQ. ID. NO. 11

5 The above-identified peptide was assembled on 4-(2'-  
4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 5. Used in analysis were Solvent A  
10 (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide gave  
product peptide having an observed retention time of 17.9  
minutes. Electrospray Mass Spectrometry (M): calculated  
15 4147.6; found 4150.2.

EXAMPLE 8Preparation of Peptide having SEQ. ID. NO. 12

20 The above-identified peptide was assembled on 4-(2'-  
4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
25 similar way to Example 5. Used in analysis were Solvent A

(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 35% to 65% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide gave  
product peptide having an observed retention time of 19.7  
5 minutes. Electrospray Mass Spectrometry (M): calculated  
4212.6; found 4213.2.

#### EXAMPLE 9

##### Preparation of Peptide having SEQ. ID. NO. 13

10

The above-identified peptide was assembled on 4-(2'-  
4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
15 cleaved from the resin, deprotected and purified in a  
similar way to Example 5. Used in analysis were Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 50% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide gave  
20 product peptide having an observed retention time of 16.3  
minutes. Electrospray Mass Spectrometry (M): calculated  
4262.7; found 4262.4.

#### EXAMPLE 10

25

##### Preparation of Peptide having SEQ. ID. NO. 14

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 5. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4172.6

15

EXAMPLE 11Preparation of Peptide having SEQ. ID. NO. 15

20

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 5. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in

25

Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4224.7.

5

#### EXAMPLE 12

##### Preparation of Peptide having SEQ. ID. NO. 16

The above-identified peptide is assembled on 4-(2'-4'-  
10 dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 5. Used in analysis are Solvent A  
15 (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
20 calculated 4172.6

#### EXAMPLE 13

##### Preparation of Peptide having SEQ. ID. NO. 17

25 The above-identified peptide is assembled on 4-(2'-4'-



dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
5 similar way to Example 5. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
10 product peptide. Electrospray Mass Spectrometry (M):  
calculated 4186.6

#### EXAMPLE 14

##### Preparation of Peptide having SEQ. ID. NO. 18

15

The above-identified peptide is assembled on 4-(2'-4'-  
dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
20 cleaved from the resin, deprotected and purified in a  
similar way to Example 5. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
25 then carried out to determine the retention time of the

product peptide. Electrospray Mass Spectrometry (M):  
calculated 4200.7

#### EXAMPLE 15

##### 5      Preparation of Peptide having SEQ. ID. NO. 19

The above-identified peptide is assembled on 4-(2'-4'-  
dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
10 Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 5. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
15 Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 4200.7

##### 20      EXAMPLE 16

##### Preparation of Peptide having SEQ. ID. NO. 20

The above-identified peptide is assembled on 4-(2'-4'-  
dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
25 norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using

Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 5. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).

5 Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 4202.7.

10

#### EXAMPLE 17

##### Preparation of Peptide having SEQ. ID. NO. 21

The above-identified peptide is assembled on 4-(2'-4'-  
15 dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 5. Used in analysis are Solvent A  
20 (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
25 calculated 4145.6.

EXAMPLE 18Preparation of Peptide having SEQ. ID. NO. 22

5           The above-identified peptide is assembled on 4-(2'-4'-  
dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
10 similar way to Example 5. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
15 product peptide. Electrospray Mass Spectrometry (M):  
calculated 4184.6.

EXAMPLE 19Preparation of Peptide having SEQ. ID. NO. 23

20           The above-identified peptide is assembled on 4-(2'-4'-  
dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
25 cleaved from the resin, deprotected and purified in a

similar way to Example 5. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 4145.6.

10

EXAMPLE 20Preparation of Peptide having SEQ. ID. NO. 24

The above-identified peptide is assembled on 4-(2'-4'-  
dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 5. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 4224.7.

25

EXAMPLE 21Preparation of Peptide having SEQ. ID. NO. 25

The above-identified peptide is assembled on 4-(2'-4'-  
5 dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 5. Used in analysis are Solvent A  
10 (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
15 calculated 4172.6.

EXAMPLE 22Preparation of Peptide having SEQ. ID. NO. 26

20 The above-identified peptide is assembled on 4-(2'-4'-  
dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
25 similar way to Example 5. Used in analysis are Solvent A

(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
5 product peptide. Electrospray Mass Spectrometry (M):  
calculated 4115.5.

#### EXAMPLE 23

##### 10 Preparation of Peptide having SEQ. ID. NO. 27

The above-identified peptide is assembled on 4-(2'-4'-  
dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
15 Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 5. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
20 Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 4188.6.

25

#### EXAMPLE 24

Preparation of Peptide having SEQ. ID. NO. 28

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide

5 norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 5. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).

10 Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4131.6.

15

EXAMPLE 25Preparation of Peptide having SEQ. ID. NO. 29

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide

20 norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 5. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).

25



Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M):  
5 calculated 4172.6.

#### EXAMPLE 26

##### Preparation of Peptide having SEQ. ID. NO. 30

10 The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.),  
15 cleaved from the resin, deprotected and purified in a similar way to Example 5. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the  
20 product peptide. Electrospray Mass Spectrometry (M):  
calculated 4145.6.

#### EXAMPLE 27

##### Preparation of Peptide having SEQ. ID. NO. 31

25

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.),  
5 cleaved from the resin, deprotected and purified in a similar way to Example 5. Additional double couplings are required at the thioproline positions 38, 37, 36 and 31. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient  
10 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4266.8.

15

EXAMPLE 28Preparation of Peptide having SEQ. ID. NO. 32

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
20 norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 5. Additional double couplings are required at the thioproline positions 38, 37 and 36. Used  
25 in analysis are Solvent A (0.1% TFA in water) and Solvent B

(0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M):  
5 calculated 4246.8.

#### EXAMPLE 29

##### Preparation of Peptide having SEQ. ID. NO. 33

10 The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.),  
15 cleaved from the resin, deprotected and purified in a similar way to Example 5. Additional double couplings are required at the homoproline positions 38, 37, 36 and 31. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the  
20 lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4250.8.

25

#### EXAMPLE 30

Preparation of Peptide having SEQ. ID. NO. 34

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 5. Additional double couplings are required at the homoproline positions 38, 37, and 36. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4234.8.

EXAMPLE 31Preparation of Peptide having SEQ. ID. NO. 35

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 5. Additional double couplings are required at the thioproline positions 38, 37, 36 and 31.

Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4209.8.

### EXAMPLE 32

#### Preparation of Peptide having SEQ. ID. NO. 36

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 5. Additional double couplings are required at the homoproline positions 38, 37, 36 and 31. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4193.7.

### EXAMPLE 33

Preparation of Peptide having SEQ. ID. NO. 37

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
5 norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 5. Additional double couplings are  
required at the N-methylalanine positions 38, 37, 36 and  
10 31. Used in analysis are Solvent A (0.1% TFA in water) and  
Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient  
30% to 60% Solvent B in Solvent A over 30 minutes) of the  
lyophilized peptide is then carried out to determine the  
retention time of the product peptide. Electrospray Mass  
15 Spectrometry (M): calculated 3858.2.

EXAMPLE 34Preparation of Peptide having SEQ. ID. NO. 38

20 The above-identified peptide is assembled on 4-(2'-4'-  
dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
25 similar way to Example 5. Additional double couplings are

required at the N-methylalanine positions 38, 37 and 36. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3940.3.

10

EXAMPLE 35Preparation of Peptide having SEQ. ID. NO. 39

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide :  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 5. Additional double couplings are  
required at the N-methylalanine positions 38, 37, 36 and  
31. Used in analysis are Solvent A (0.1% TFA in water) and  
Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient  
30% to 60% Solvent B in Solvent A over 30 minutes) of the  
lyophilized peptide is then carried out to determine the  
retention time of the product peptide. Electrospray Mass  
Spectrometry (M): calculated 3801.1.

EXAMPLE 36

Preparation of C-terminal carboxylic acid Peptides  
corresponding to the above C-terminal amide sequences.

5

The above peptides of Examples 5 to 35 are assembled on the so called Wang resin (p-alkoxybenzylalcohol resin (Bachem, 0.54 mmole/g)) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin,

10

deprotected and purified in a similar way to Example 5.

Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry provides an experimentally determined (M).

15

EXAMPLE 37

20

Preparation of Peptide having SEQ ID NO. 7

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly  
Gly-NH<sub>2</sub> [SEQ. ID. NO. 7]

25

The above amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide



norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.). In general, single-coupling cycles were used throughout the synthesis and Fast Moc (HBTU activation) chemistry was employed. Deprotection (Fmoc group removal) of the growing peptide chain was achieved using piperidine. Final deprotection of the completed peptide resin was achieved using a mixture of triethylsilane (0.2 mL), ethanedithiol (0.2 mL), anisole (0.2 mL), water (0.2 mL) and trifluoroacetic acid (15 mL) according to standard methods (Introduction to Cleavage Techniques, Applied Biosystems, Inc.) The peptide was precipitated in ether/water (50 mL) and centrifuged. The precipitate was reconstituted in glacial acetic acid and lyophilized. The lyophilized peptide was dissolved in water). Crude purity was about 75%.

Used in purification steps and analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). The solution containing peptide was applied to a preparative C-18 column and purified (10% to 40% Solvent B in Solvent A over 40 minutes). Purity of fractions was determined isocratically using a C-18 analytical column. Pure fractions were pooled furnishing the above-identified peptide. Analytical RP-HPLC (gradient 30% to 50% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide

gave product peptide having an observed retention time of 18.9 minutes. Electrospray Mass Spectrometry (M): calculated 3408.0; found 3408.9.

5

EXAMPLE 38Preparation of Peptide having SEQ ID NO. 40

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
10 Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 40]

The above amidated peptide was assembled on 4-(2'-4'-  
dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
15 norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 37. Used in analysis were Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
20 Analytical RP-HPLC (gradient 30% to 40% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide gave  
product peptide having an observed retention time of 17.9  
minutes. Electrospray Mass Spectrometry (M): calculated  
3294.7; found 3294.8.

25

EXAMPLE 39Preparation of Peptide having SEQ ID NO. 41

5

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 41]

10

15

20

The above-identified amidated peptide was assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 37. Used in analysis were Solvent  
A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 29% to 36% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide gave  
product peptide having an observed retention time of 20.7  
minutes. Electrospray Mass Spectrometry (M): calculated  
3237.6; found 3240.

EXAMPLE 40

25

Preparation of Peptide having SEQ ID NO. 42

His Ala Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 42]

5

The above amidated peptide was assembled on 4-(2'-4'-  
dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
10 cleaved from the resin, deprotected and purified in a  
similar way to Example 37. Used in analysis were Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 36% to 46% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide gave  
15 product peptide having an observed retention time of 15.2  
minutes. Electrospray Mass Spectrometry (M): calculated  
3251.6; found 3251.5.

#### EXAMPLE 41

20

#### Preparation of Peptide having SEQ ID NO. 43

His Gly Glu Gly Ala Phe Thr Ser Asp Leu Ser Lys Gln  
Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys  
25 Asn-NH<sub>2</sub> [SEQ. ID. NO. 43]

The above amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
5 Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 37. Used in analysis were Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 36% to 46% Solvent B in  
10 Solvent A over 30 minutes) of the lyophilized peptide gave  
product peptide having an observed retention time of 13.1  
minutes. Electrospray Mass Spectrometry (M): calculated  
3207.6; found 3208.3.

15

EXAMPLE 42Preparation of Peptide having SEQ ID NO. 44

His Gly Glu Gly Thr Ala Thr Ser Asp Leu Ser Lys Gln Leu Glu  
20 Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 44]

The above amidated peptide was assembled on 4-(2'-4'-  
dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
25 norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using

Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 37. Used in analysis were Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
5 Analytical RP-HPLC (gradient 35% to 45% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide gave  
product peptide having an observed retention time of 12.8  
minutes. Electrospray Mass Spectrometry (M): calculated  
3161.5; found 3163.

10

#### EXAMPLE 43

##### Preparation of Peptide having SEQ ID NO. 45

15 His Gly Glu Gly Thr Phe Thr Ala Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 45]

The above-identified amidated peptide was assembled on  
20 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 37. Used in analysis were Solvent  
25 A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).

Analytical RP-HPLC (gradient 36% to 46% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 15.2 minutes. Electrospray Mass Spectrometry (M): calculated 3221.6; found 3222.7.

#### EXAMPLE 44

##### Preparation of Peptide having SEQ ID NO. 46

His Gly Glu Gly Thr Phe Thr Ser Asp Ala Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 46]

The above-identified amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 34% to 44% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 14.3 minutes. Electrospray Mass Spectrometry (M): calculated

3195.5; found 3199.4.

EXAMPLE 45

5           Preparation of Peptide having SEQ ID NO. 47

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ala Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 47]

10       The above-identified amidated peptide was assembled on 4-  
(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
15       cleaved from the resin, deprotected and purified in a  
similar way to Example 37. Used in analysis were Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 38% to 48% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide gave  
20       product peptide having an observed retention time of 15.7  
minutes. Electrospray Mass Spectrometry (M): calculated  
3221.6; found 3221.6.

EXAMPLE 46

25           Preparation of Peptide having SEQ ID NO. 48



His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Ala Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>

[SEQ. ID. NO. 48]

5           The above-identified amidated peptide was assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc           aminomethyl           phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
10   a similar way to Example 37. Used in analysis were Solvent  
A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 38% to 48% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide gave  
product peptide having an observed retention time of 18.1  
15   minutes. Electrospray Mass Spectrometry (M): calculated  
3180.5; found 3180.9.

#### EXAMPLE 47

#### 20           Preparation of Peptide having SEQ ID NO. 49

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Ala Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>

[SEQ. ID. NO. 49]

25

The above-identified amidated peptide was assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc           aminomethyl           phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)

using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Compound 1. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
5 Analytical RP-HPLC (gradient 36% to 46% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 17.0 minutes. Electrospray Mass Spectrometry (M): calculated 3180.6; found 3182.8.

10

EXAMPLE 48Preparation of Peptide having SEQ ID NO. 50

15 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Ala Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 50]

The above-identified amidated peptide was assembled on  
20 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 37. Used in analysis were Solvent  
25 A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).

Analytical RP-HPLC (gradient 32% to 42% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 14.9 minutes. Electrospray Mass Spectrometry (M): calculated 3195.5; found 3195.9.

#### EXAMPLE 49

##### Preparation of Peptide having SEQ ID NO. 51

10

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Ala  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 51]

15

The above-identified amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in

20

a similar way to Example 37. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 37% to 47% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 17.9

25

minutes. Electrospray Mass Spectrometry (M): calculated

3179.6; found 3179.0.

#### EXAMPLE 50

5

#### Preparation of Peptide having SEQ ID NO. 52

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Ala Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
10 [SEQ. ID. NO. 52]

The above-identified amidated peptide was assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
15 using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 37. Used in analysis were Solvent  
A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 37% to 47% Solvent B in  
20 Solvent A over 30 minutes) of the lyophilized peptide gave  
product peptide having an observed retention time of 14.3  
minutes. Electrospray Mass Spectrometry (M): calculated  
3179.6; found 3180.0.

25

#### EXAMPLE 51

#### Preparation of Peptide having SEQ ID NO. 53

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Ala Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 53]

5           The above-identified peptide was assembled on 4-(2'-  
4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
10       similar way to Example 37. Used in analysis were Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 37% to 47% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide gave  
product peptide having an observed retention time of 13.7  
15       minutes. Electrospray Mass Spectrometry (M): calculated  
3179.6; found 3179.0.

#### EXAMPLE 52

20           Preparation of Peptide having SEQ ID NO. 54

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Ala Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 54]

25

The above-identified amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 35% to 45% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 14.0 minutes. Electrospray Mass Spectrometry (M): calculated 3209.6; found 3212.8.

#### EXAMPLE 53

##### Preparation of Peptide having SEQ ID NO. 55

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Ala Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 55]

The above-identified amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems,

Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 38% to 48% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 14.3 minutes. Electrospray Mass Spectrometry (M): calculated 3152.5; found 3153.5.

10

EXAMPLE 54Preparation of Peptide having SEQ ID NO. 56

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
15 Glu Glu Ala Val Arg Ala Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 56]

The above-identified amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
20 Analytical RP-HPLC (gradient 35% to 45% Solvent B in  
25

Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 12.1 minutes. Electrospray Mass Spectrometry (M): calculated 3195.5; found 3197.7.

5

EXAMPLE 55

Preparation of Peptide having SEQ ID NO. 57

10 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Ala Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 57]

The above-identified amidated peptide was assembled on  
15 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 37. Used in analysis were Solvent  
20 A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 38% to 48% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide gave  
product peptide having an observed retention time of 10.9  
minutes. Electrospray Mass Spectrometry (M): calculated  
25 3179.6; found 3180.5.



EXAMPLE 56Preparation of Peptide having SEQ ID NO. 58

5

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Ala Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 58]

10

The above-identified amidated peptide was assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
15 a similar way to Example 37. Used in analysis were Solvent  
A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 32% to 42% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide gave  
product peptide having an observed retention time of 17.5  
20 minutes. Electrospray Mass Spectrometry (M): calculated  
3161.5; found 3163.0.

EXAMPLE 57

25

Preparation of Peptide having SEQ ID NO. 59

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Ala Lys Asn-NH<sub>2</sub>

[SEQ. ID. NO. 59]

The above-identified amidated peptide was assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
5 acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 37. Used in analysis were Solvent  
A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
10 Analytical RP-HPLC (gradient 32% to 42% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide gave  
product peptide having an observed retention time of 19.5  
minutes. Electrospray Mass Spectrometry (M): calculated  
3195.5; found 3199.

15

#### EXAMPLE 58

##### Preparation of Peptide having SEQ ID NO. 60

20 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Ala Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 60]

The above-identified amidated peptide was assembled on  
25 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy

acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 38% to 48% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 14.5 minutes. Electrospray Mass Spectrometry (M): calculated 3180.5; found 3183.7.

#### EXAMPLE 59

##### Preparation of Peptide having SEQ ID NO. 61

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Ala-NH<sub>2</sub>  
[SEQ. ID. NO. 61]

The above-identified amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis were Solvent

A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 34% to 44% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide gave  
product peptide having an observed retention time of 22.8  
5 minutes. Electrospray Mass Spectrometry (M): calculated  
3194.6; found 3197.6.

#### EXAMPLE 60

##### 10 Preparation of Peptide having SEQ ID NO. 62

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly  
Pro Ser Ser Gly Ala Pro Pro Pro-NH<sub>2</sub> [SEQ. ID. NO. 62]

15

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
20 Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 37. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
25 then carried out to determine the retention time of the

product peptide. Electrospray Mass Spectrometry (M):  
calculated 4099.6.

#### EXAMPLE 61

5

#### Preparation of Peptide having SEQ ID NO. 63

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly  
10 Pro Ser Ser Gly Ala Pro Pro Pro-NH<sub>2</sub> [SEQ. ID. NO. 63]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
15 using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 37. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
20 Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 4042.5.

25

#### EXAMPLE 62

Preparation of Peptide having SEQ ID NO. 64

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
5 Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly  
Pro Ser Ser Gly Ala Pro Pro-NH<sub>2</sub> [SEQ. ID. NO. 64]

The above-identified peptide is assembled on 4-(2'-4'-  
dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
10 norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 37. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
15 Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 4002.4

20

EXAMPLE 63Preparation of Peptide having SEQ ID NO. 65

25 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu

Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly  
Pro Ser Ser Gly Ala Pro Pro-NH<sub>2</sub> [SEQ. ID. NO. 65]

5 The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 37. Used in analysis are Solvent A  
10 (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
15 calculated 3945.4.

#### EXAMPLE 64

##### Preparation of Peptide having SEQ ID NO. 66

20

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln  
Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn  
Gly Gly Pro Ser Ser Gly Ala Pro-NH<sub>2</sub> [SEQ. ID. NO. 66]

25

The above-identified amidated peptide is assembled on

4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
5 a similar way to Example 37. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
10 product peptide. Electrospray Mass Spectrometry (M):  
calculated 3905.3.

#### EXAMPLE 65

##### 15 Preparation of Peptide having SEQ ID NO. 67

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly  
Pro Ser Ser Gly Ala Pro-NH<sub>2</sub> [SEQ. ID. NO. 67]

20

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
25 Inc.), cleaved from the resin, deprotected and purified in



a similar way to Example 37. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is  
5 then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3848.2.

#### EXAMPLE 66

10

#### Preparation of Peptide having SEQ ID NO. 68

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly  
15 Pro Ser Ser Gly Ala-NH<sub>2</sub> [SEQ. ID. NO. 68]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
20 using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
25 Solvent A over 30 minutes) of the lyophilized peptide is

then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3808.2.

5

EXAMPLE 67Preparation of Peptide having SEQ ID NO. 69

10 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly  
Pro Ser Ser Gly Ala-NH<sub>2</sub> [SEQ. ID. NO. 69]

The above-identified amidated peptide is assembled on  
15 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 37. Used in analysis are Solvent A  
20 (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
25 calculated 3751.1.

EXAMPLE 68Preparation of Peptide having SEQ ID NO. 70

5

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly  
Pro Ser Ser Gly-NH<sub>2</sub> [SEQ. ID. NO. 70]

10

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
15 a similar way to Example 37. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
20 product peptide. Electrospray Mass Spectrometry (M):  
calculated 3737.1.

EXAMPLE 69

25

Preparation of Peptide having SEQ ID NO. 71

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly  
Pro Ser Ser Gly-NH<sub>2</sub> [SEQ. ID. NO. 71]

5

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
10 Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 37. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
15 then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3680.1.

#### EXAMPLE 70

20

#### Preparation of Peptide having SEQ ID NO. 72

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly  
25 Pro Ser Ser-NH<sub>2</sub> [SEQ. ID. NO. 72]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3680.1

15

EXAMPLE 71Preparation of Peptide having SEQ ID NO. 73

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly  
Pro Ser Ser-NH<sub>2</sub> [SEQ. ID. NO. 73]

25

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis are Solvent A

(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3623.0.

#### EXAMPLE 72

##### Preparation of Peptide having SEQ ID NO. 74

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly  
Pro Ser-NH<sub>2</sub> [SEQ. ID. NO. 74]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 37. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the

product peptide. Electrospray Mass Spectrometry (M):  
calculated 3593.0

### EXAMPLE 73

5

#### Preparation of Peptide having SEQ ID NO. 75

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly  
10 Pro Ser-NH<sub>2</sub> [SEQ. ID. NO. 75]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
15 using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 37. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
20 Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3535.9

25

### EXAMPLE 74

Preparation of Peptide having SEQ ID NO. 76

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
5 Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly  
Pro-NH<sub>2</sub> [SEQ. ID. NO. 76]

The above-identified peptide is assembled on 4-(2'-4'-  
dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
10 norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 37. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
15 Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3505.9.

20

EXAMPLE 75Preparation of Peptide having SEQ ID NO. 77

25 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu



Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly  
Pro-NH<sub>2</sub> [SEQ. ID. NO. 77]

5 The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 37. Used in analysis are Solvent A  
10 (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
15 calculated 3448.8.

#### EXAMPLE 76

##### Preparation of Peptide having SEQ ID NO. 78

20

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly  
Gly-NH<sub>2</sub> [SEQ. ID. NO. 78]

25

The above-identified peptide is assembled on 4-(2'-4'-

dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
5 similar way to Example 37. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
10 product peptide. Electrospray Mass Spectrometry (M):  
calculated 3351.7.

#### EXAMPLE 77

15

##### Preparation of Peptide having SEQ ID NO. 79

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly-NH<sub>2</sub>  
20 [SEQ. ID. NO. 79]

The above-identified peptide is assembled on 4-(2'-4'-  
dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
25 Fmoc-protected amino acids (Applied Biosystems, Inc.),

cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3351.8.

10

EXAMPLE 78Preparation of Peptide having SEQ ID NO. 80

15

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly-NH<sub>2</sub>  
[SEQ. ID. NO. 80]

20

25

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in

Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3294.7.

5

EXAMPLE 79Preparation of Peptide having SEQ ID NO. 81

10 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly  
tPro Ser Ser Gly Ala tPro tPro tPro-NH<sub>2</sub> [SEQ. ID. NO. 81]

The above-identified amidated peptide is assembled on  
15 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 37. Double couplings are required  
20 at residues 37,36 and 31. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
25 product peptide. Electrospray Mass Spectrometry (M):

calculated 4197.1.

#### EXAMPLE 80

##### 5           Preparation of Peptide having SEQ ID NO. 82

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly  
Pro Ser Ser Gly Ala tPro tPro tPro-NH<sub>2</sub> [SEQ. ID. NO. 82]

10

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
15 Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 37. Double couplings are required  
at residues 37, 36 and 31. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
20 Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 4179.1.

25

#### EXAMPLE 81

Preparation of Peptide having SEQ ID NO. 83

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
5 Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly  
NMeala Ser Ser Gly Ala Pro Pro-NH<sub>2</sub> [SEQ. ID. NO. 83]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
10 acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 37. Double couplings are required  
at residues 36 and 31. Used in analysis are Solvent A (0.1%  
15 TFA in water) and Solvent B (0.1% TFA in ACN). Analytical  
RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30  
minutes) of the lyophilized peptide is then carried out to  
determine the retention time of the product peptide.  
Electrospray Mass Spectrometry (M): calculated 3948.3.

20

EXAMPLE 82Preparation of Peptide having SEQ ID NO. 84

25 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu

Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly  
NMeala Ser Ser Gly Ala NMeala Nmeala-NH<sub>2</sub> [SEQ. ID. NO. 84]

5 The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
10 a similar way to Example 37. Double couplings are required  
at residues 36 and 31. Used in analysis are Solvent A (0.1%  
TFA in water) and Solvent B (0.1% TFA in ACN). Analytical  
RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30  
minutes) of the lyophilized peptide is then carried out to  
determine the retention time of the product peptide.  
15 Electrospray Mass Spectrometry (M): calculated 3840.1.

### EXAMPLE 83

#### Preparation of Peptide having SEQ ID NO. 85

20

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly  
hPro Ser Ser Gly Ala hPro hPro-NH<sub>2</sub> [SEQ. ID. NO. 85]

25

The above-identified amidated peptide is assembled on

4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
5 a similar way to Example 37. Double couplings are required  
at residues 36 and 31. Used in analysis are Solvent A (0.1%  
TFA in water) and Solvent B (0.1% TFA in ACN). Analytical  
RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30  
minutes) of the lyophilized peptide is then carried out to  
10 determine the retention time of the product peptide.  
Electrospray Mass Spectrometry (M): calculated 4050.1.

#### EXAMPLE 84

##### 15 Preparation of Peptide having SEQ ID NO. 86

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly  
hPro Ser Ser Gly Ala hPro-NH<sub>2</sub> [SEQ. ID. NO. 86]

20

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
25 Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 37. A double coupling is required



at residue 31. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3937.1

#### EXAMPLE 85

#### 10      Preparation of Peptide having SEQ ID NO. 87

Arg Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly  
Pro Ser Ser Gly Ala-NH<sub>2</sub> [SEQ. ID. NO. 87]

15

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the

25

product peptide. Electrospray Mass Spectrometry (M):  
calculated 3827.2.

#### EXAMPLE 86

5

#### Preparation of Peptide having SEQ ID NO. 88

His Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly  
10 Gly-NH<sub>2</sub> [SEQ. ID. NO. 88]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
15 using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 37. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
20 Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3394.8.

25

#### EXAMPLE 87

Preparation of Peptide having SEQ ID NO. 89

His Gly Glu Gly Thr Naphthylala Thr Ser Asp Leu Ser Lys Gln  
5 Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys  
Asn-NH<sub>2</sub> [SEQ. ID. NO. 89]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
10 acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 37. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
15 Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3289.5.

20

EXAMPLE 88Preparation of Peptide having SEQ ID NO. 90

25 His Gly Glu Gly Thr Phe Ser Ser Asp Leu Ser Lys Gln Met Glu

Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 90]

The above-identified amidated peptide is assembled on  
5 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 37. Used in analysis are Solvent A  
10 (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
15 calculated 3280.7.

#### EXAMPLE 89

##### Preparation of Peptide having SEQ ID NO. 91

20

His Gly Glu Gly Thr Phe Ser Thr Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 91]

25

The above-identified amidated peptide is assembled on

4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
5 a similar way to Example 37. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
10 product peptide. Electrospray Mass Spectrometry (M):  
calculated 3294.7.

#### EXAMPLE 90

##### 15 Preparation of Peptide having SEQ ID NO. 92

His Gly Glu Gly Thr Phe Thr Ser Glu Leu Ser Lys Gln Met Ala  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 92]

20 The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
25 a similar way to Example 37. Used in analysis are Solvent A

(0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M):  
5 calculated 3250.7.

### EXAMPLE 91

#### 10 Preparation of Peptide having SEQ ID NO. 93

His Gly Glu Gly Thr Phe Thr Ser Asp pentylgly Ser Lys Gln  
Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys  
Asn-NH<sub>2</sub> [SEQ. ID. NO. 93]

15

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.),  
20 cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is  
25 then carried out to determine the retention time of the

product peptide. Electrospray Mass Spectrometry (M):  
calculated 3253.5.

## EXAMPLE 92

5

### Preparation of Peptide having SEQ ID NO. 94

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Naphthylala Ile Glu Phe Leu Lys  
10 Asn-NH<sub>2</sub> [SEQ. ID. NO. 94]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
15 using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 37. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
20 Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3289.5.

25

## EXAMPLE 93

Preparation of Peptide having SEQ ID NO. 95

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
5 Glu Glu Ala Val Arg Leu Phe tButylgly Glu Trp Leu Lys Asn-  
NH<sub>2</sub> [SEQ. ID. NO. 95]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
10 acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 37. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
15 Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3183.4.

20

EXAMPLE 94Preparation of Peptide having SEQ ID NO. 96

25 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu



Glu Glu Ala Val Arg Leu Phe Ile Asp Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 96]

The above-identified amidated peptide is assembled on  
5 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 37. Used in analysis are Solvent A  
10 (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
15 calculated 3237.6.

#### EXAMPLE 95

##### Preparation of Peptide having SEQ ID NO. 97

20

His Gly Glu Gly Thr Phe Thr Ser Asp Ala Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly  
Pro Ser Ser-NH<sub>2</sub> [SEQ. ID. NO. 97]

25 The above-identified amidated peptide is assembled on

4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
5 a similar way to Example 37. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
10 product peptide. Electrospray Mass Spectrometry (M):  
calculated 3637.9.

#### EXAMPLE 96

##### 15 Preparation of Peptide having SEQ ID NO. 98

His Gly Glu Gly Thr Phe Thr Ser Asp Ala Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly-NH<sub>2</sub>  
[SEQ. ID. NO. 98]

20

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
25 Inc.), cleaved from the resin, deprotected and purified in

a similar way to Example 37. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3309.7.

#### EXAMPLE 97

10

#### Preparation of Peptide having SEQ ID NO. 99

His Gly Glu Gly Thr Phe Thr Ser Asp Ala Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly  
hPro Ser Ser Gly Ala hPro hPro-NH<sub>2</sub> [SEQ. ID. NO. 99]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Double couplings are required at residues 36 and 31. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30

minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3711.1.

5

EXAMPLE 98

Preparation of C-terminal carboxylic acid peptides corresponding to the above C-terminal amide sequences for  
10 SEQ ID NOS. 7, 40-61, 68-75, 78-80 and 87-96

Peptides having the sequences of SEQ ID NOS. 7, 40-61, 68-75, 78-80 and 87-96 are assembled on the so called Wang resin (p-alkoxybenzylalcohol resin (Bachem, 0.54 mmole/g))  
15 using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
20 Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry provides an experimentally determined (M).

EXAMPLE 99

Preparation of C-terminal carboxylic acid peptides  
corresponding to the above C-terminal amide sequences for  
5 SEQ ID NOS. 62-67, 76, 77 and 81-86

Peptides having the sequences of SEQ ID NOS. 62-67,  
76, 77 and 81-86 are assembled on the 2-  
chlorotritylchloride resin (200-400 mesh), 2% DVB  
10 (Novabiochem, 0.4-1.0 mmole/g)) using Fmoc-protected amino  
acids (Applied Biosystems, Inc.), cleaved from the resin,  
deprotected and purified in a similar way to Example 37.  
Used in analysis are Solvent A (0.1% TFA in water) and  
Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient  
15 30% to 60% Solvent B in Solvent A over 30 minutes) of the  
lyophilized peptide is then carried out to determine the  
retention time of the product peptide. Electrospray Mass  
Spectrometry provides an experimentally determined (M).

20

EXAMPLE 100Preparation of Peptide having SEQ ID NO. 100

Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
25 Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>

[SEQ. ID. NO. 100]

The above amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
5 norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.). In general, single-coupling cycles were used throughout the synthesis and Fast Moc (HBTU activation) chemistry was employed. Deprotection (Fmoc group removal) of the growing  
10 peptide chain was achieved using piperidine. Final deprotection of the completed peptide resin was achieved using a mixture of triethylsilane (0.2 mL), ethanedithiol (0.2 mL), anisole (0.2 mL), water (0.2 mL) and trifluoroacetic acid (15 mL) according to standard methods  
15 (Introduction to Cleavage Techniques, Applied Biosystems, Inc.) The peptide was precipitated in ether/water (50 mL) and centrifuged. The precipitate was reconstituted in glacial acetic acid and lyophilized. The lyophilized peptide was dissolved in water). Crude purity was about  
20 75%.

Used in purification steps and analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).

The solution containing peptide was applied to a preparative C-18 column and purified (10% to 40% Solvent B  
25 in Solvent A over 40 minutes). Purity of fractions was

determined isocratically using a C-18 analytical column.  
Pure fractions were pooled furnishing the above-identified  
peptide. Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
5 gave product peptide having an observed retention time of  
19.2 minutes. Electrospray Mass Spectrometry (M):  
calculated 3171.6; found 3172.

#### EXAMPLE 101

10

#### Preparation of Peptide having SEQ ID NO. 101

His Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>

15

[SEQ. ID. NO. 101]

20

The above amidated peptide was assembled on 4-(2'-4'-  
dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 100. Used in analysis were Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 36% to 46% Solvent B in  
25 Solvent A over 30 minutes) of the lyophilized peptide gave

product peptide having an observed retention time of 14.9 minutes. Electrospray Mass Spectrometry (M): calculated 3179.6; found 3180.

5

EXAMPLE 102Preparation of Peptide having SEQ ID NO. 102

His Gly Glu Ala Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
10 Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 102]

The above amidated peptide was assembled on 4-(2'-4'-  
dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
15 norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 100. Used in analysis were Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
20 Analytical RP-HPLC (gradient 37% to 47% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide gave  
product peptide having an observed retention time of 12.2  
minutes. Electrospray Mass Spectrometry (M): calculated  
3251.6; found 3253.3.

25



EXAMPLE 103Preparation of Peptide having SEQ ID NO. 103

5 His Gly Glu Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 103]

The above amidated peptide was assembled on 4-(2'-4'-  
10 dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 100. Used in analysis were Solvent A  
15 (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 35% to 45% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide gave  
product peptide having an observed retention time of 16.3  
minutes. Electrospray Mass Spectrometry (M): calculated  
20 3193.6; found 3197.

EXAMPLE 104Preparation of Peptide having SEQ ID NO. 104

25

Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 104]

5           The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
10   a similar way to Example 100. Used in analysis are Solvent  
A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
15   product peptide. Electrospray Mass Spectrometry (M):  
calculated 3228.6.

#### EXAMPLE 105

20           Preparation of Peptide having SEQ ID NO. 105

His Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 105]

25

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3234.7.

#### EXAMPLE 106

##### Preparation of Peptide having SEQ ID NO. 106

His Gly Glu Ala Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 106]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems,

Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).

Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3308.7.

#### EXAMPLE 107

##### Preparation of Peptide having SEQ ID NO. 107

His Gly Glu Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 107]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in

Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3250.7

5

EXAMPLE 108

Preparation of Peptide having SEQ ID NO. 108

10 His Gly Glu Gly Thr Phe Thr Ser Asp Ala Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 108]

The above-identified amidated peptide is assembled on  
15 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 100. Used in analysis are Solvent  
20 A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
25 calculated 3252.6.

EXAMPLE 109Preparation of Peptide having SEQ ID NO. 109

5

Ala Ala Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 109]

10

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
15 a similar way to Example 100. Used in analysis are Solvent  
A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN)..  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
20 product peptide. Electrospray Mass Spectrometry (M):  
calculated 3200.6.

EXAMPLE 110

25

Preparation of Peptide having SEQ ID NO. 110

Ala Ala Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 110]

5           The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
10       a similar way to Example 100. Used in analysis are Solvent  
A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
15       product peptide. Electrospray Mass Spectrometry (M):  
calculated 3143.5.

#### EXAMPLE 111

20

#### Preparation of Peptide having SEQ ID NO. 111

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
25       [SEQ. ID. NO. 111]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3214.6.

#### EXAMPLE 112

##### Preparation of Peptide having SEQ ID NO. 112

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 112]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)



using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).

5 Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3157.5.

10

### EXAMPLE 113

#### Preparation of Peptide having SEQ ID NO. 113

15 Ala Gly Asp Gly Ala Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 113]

The above-identified amidated peptide is assembled on  
20 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 100. Used in analysis are Solvent  
25 A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).

Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M):  
5 calculated 3184.6.

#### EXAMPLE 114

##### Preparation of Peptide having SEQ ID NO. 114

10

Ala Gly Asp Gly Ala Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 114]

15

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in  
20 a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).

20

Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the  
25 product peptide. Electrospray Mass Spectrometry (M):

calculated 3127.5.

EXAMPLE 115

5           Preparation of Peptide having SEQ ID NO. 115

Ala Gly Asp Gly Thr NaphthylAla Thr Ser Asp Leu Ser Lys Gln  
Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys  
Asn-NH<sub>2</sub> [SEQ. ID. NO. 115]

10

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
15 Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 100. Used in analysis are Solvent  
A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
20 then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3266.4.

EXAMPLE 116

25

Preparation of Peptide having SEQ ID NO. 116

Ala Gly Asp Gly Thr Naphthylala Thr Ser Asp Leu Ser Lys Gln  
Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys  
5 Asn-NH<sub>2</sub> [SEQ. ID. NO. 116]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
10 using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 100. Used in analysis are Solvent  
A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
15 Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3209.4.

20

EXAMPLE 117Preparation of Peptide having SEQ ID NO. 117

Ala Gly Asp Gly Thr Phe Ser Ser Asp Leu Ser Lys Gln Met Glu  
25 Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>

[SEQ. ID. NO. 117]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
5 acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 100. Used in analysis are Solvent  
A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
10 Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3200.6.

15

#### EXAMPLE 118

##### Preparation of Peptide having SEQ ID NO. 118

20 Ala Gly Asp Gly Thr Phe Ser Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 118]

The above-identified amidated peptide is assembled on  
25 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy

acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3143.5.

#### EXAMPLE 119

##### Preparation of Peptide having SEQ ID NO. 119

Ala Gly Asp Gly Thr Phe Thr Ala Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 119]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in

a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3198.6.

#### EXAMPLE 120

##### Preparation of Peptide having SEQ ID NO. 120

Ala Gly Asp Gly Thr Phe Thr Ala Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 120]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is

then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3141.5.

5

EXAMPLE 121Preparation of Peptide having SEQ ID NO. 121

Ala Gly Asp Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Met Glu  
10 Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 121]

The above-identified peptide is assembled on 4-(2'-4'-  
dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
15 norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 100. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
20 Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3170.6.

25



EXAMPLE 122Preparation of Peptide having SEQ ID NO. 122

5     Ala Gly Asp Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Leu Glu  
      Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
      [SEQ. ID. NO. 122]

      The above-identified amidated peptide is assembled on  
10    4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
      acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
      using Fmoc-protected amino acids (Applied Biosystems,  
      Inc.), cleaved from the resin, deprotected and purified in  
      a similar way to Example 100. Used in analysis are Solvent  
15    A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
      Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
      Solvent A over 30 minutes) of the lyophilized peptide is  
      then carried out to determine the retention time of the  
      product peptide. Electrospray Mass Spectrometry (M):  
20    calculated 3113.5.

EXAMPLE 123Preparation of Peptide having SEQ ID NO. 123

25

Ala Gly Asp Gly Thr Phe Thr Ser Glu Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 123]

5           The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
10   a similar way to Example 100. Used in analysis are Solvent  
A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
15   product peptide. Electrospray Mass Spectrometry (M):  
calculated 3228.6.

#### EXAMPLE 124

20           Preparation of Peptide having SEQ ID NO. 124

Ala Gly Asp Gly Thr Phe Thr Ser Glu Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 124]

25

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3171.6.

#### EXAMPLE 125

15

#### Preparation of Peptide having SEQ ID NO. 125

Ala Gly Asp Gly Thr Phe Thr Ser Asp Ala Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 125]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems,

Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3172.5.

10

EXAMPLE 126Preparation of Peptide having SEQ ID NO. 126

Ala Gly Asp Gly Thr Phe Thr Ser Asp Ala Ser Lys Gln Leu Glu  
15 Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 126]

The above-identified amidated peptiden is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
20 Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
25

Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3115.4.

5

#### EXAMPLE 127

##### Preparation of Peptide having SEQ ID NO. 127

10 Ala Gly Asp Gly Thr Phe Thr Ser Asp Pentylgly Ser Lys Gln  
Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys  
Asn-NH<sub>2</sub> [SEQ. ID. NO. 127]

The above-identified amidated peptide is assembled on  
15 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 100. Used in analysis are Solvent  
20 A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
25 calculated 3230.4.

EXAMPLE 128Preparation of Peptide having SEQ ID NO. 128

5

Ala Gly Asp Gly Thr Phe Thr Ser Asp Pentylgly Ser Lys Gln  
Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys  
Asn-NH<sub>2</sub> [SEQ. ID. NO. 128]

10

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
15 a similar way to Example 100. Used in analysis are Solvent  
A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
20 product peptide. Electrospray Mass Spectrometry (M):  
calculated 3198.6.

EXAMPLE 129

25

Preparation of Peptide having SEQ ID NO. 129

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ala Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 129]

5

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
10 Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 100. Used in analysis are Solvent  
A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
15 then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3141.5.

#### EXAMPLE 130

20

#### Preparation of Peptide having SEQ ID NO. 130

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ala Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
25 [SEQ. ID. NO. 130]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3157.5.

15

EXAMPLE 131Preparation of Peptide having SEQ ID NO. 131

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Ala Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 131]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)



using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).

- 5 Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3100.4.

10

#### EXAMPLE 132

##### Preparation of Peptide having SEQ ID NO. 132

- 15 Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Ala Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 132]

- 20 The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent  
25 A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).

Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M):

5       calculated 3157.6.

### EXAMPLE 133

#### Preparation of Peptide having SEQ ID NO. 133

10

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Ala Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 133]

15

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).

20

Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M):

25

calculated 3100.5.

EXAMPLE 134

5           Preparation of Peptide having SEQ ID NO. 134

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Ala Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 134]

10

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
15 Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 100. Used in analysis are Solvent  
A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
20 then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3100.5.

EXAMPLE 135

25

Preparation of Peptide having SEQ ID NO. 135

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Ala Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>

5 [SEQ. ID. NO. 135]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
10 using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 100. Used in analysis are Solvent  
A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
15 Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3154.5.

20

EXAMPLE 136Preparation of Peptide having SEQ ID NO. 136

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Ala Glu  
25 Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>

[SEQ. ID. NO. 136]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
5 acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 100. Used in analysis are Solvent  
A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
10 Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3115.5.

15

#### EXAMPLE 137

##### Preparation of Peptide having SEQ ID NO. 137

20 Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln  
Pentylgly Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu  
Lys Asn-NH<sub>2</sub> [SEQ. ID. NO. 137]

The above-identified amidated peptide is assembled on  
25 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy

acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3212.4.

#### EXAMPLE 138

##### Preparation of Peptide having SEQ ID NO. 138

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln  
Pentylgly Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu  
Lys Asn-NH<sub>2</sub> [SEQ. ID. NO. 138]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent

A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
5 product peptide. Electrospray Mass Spectrometry (M):  
calculated 3173.4.

#### EXAMPLE 139

##### Preparation of Peptide having SEQ ID NO. 139

10

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Ala  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 139]

15

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 100. Used in analysis are Solvent  
20 A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).

20

Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
25 calculated 3156.6.

EXAMPLE 140Preparation of Peptide having SEQ ID NO. 140

5

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Ala  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 140]

10

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
15 a similar way to Example 100. Used in analysis are Solvent  
A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
20 product peptide. Electrospray Mass Spectrometry (M):  
calculated 3099.5.

EXAMPLE 141

25

Preparation of Peptide having SEQ ID NO. 141



Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Ala Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 141]

5

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
10 Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 100. Used in analysis are Solvent  
A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
15 then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3156.6.

#### EXAMPLE 142

20

#### Preparation of Peptide having SEQ ID NO. 142

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Ala Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
25 [SEQ. ID. NO. 142]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3099.5.

#### EXAMPLE 143

15

#### Preparation of Peptide having SEQ ID NO. 143

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Ala Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 143]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems,

Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).

Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3156.6.

10

EXAMPLE 144Preparation of Peptide having SEQ ID NO. 144

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
15 Glu Ala Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 144]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
20 Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
25

Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3099.5.

5

#### EXAMPLE 145

##### Preparation of Peptide having SEQ ID NO. 145

10 Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Ala Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 145]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
15 acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
20 Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3186.6.

25

EXAMPLE 146Preparation of Peptide having SEQ ID NO. 146

5     Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Ala Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 146]

10     The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 100. Used in analysis are Solvent  
15     A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
20     calculated 3129.5.

EXAMPLE 147Preparation of Peptide having SEQ ID NO. 147

25     Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu

Glu Glu Ala Val Ala Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 147]

5 The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 100. Used in analysis are Solvent  
10 A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
15 calculated 3129.5.

#### EXAMPLE 148

##### Preparation of Peptide having SEQ ID NO. 148

20

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Ala Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 148]

25 The above-identified amidated peptide is assembled on

4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
5 a similar way to Example 100. Used in analysis are Solvent  
A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
10 product peptide. Electrospray Mass Spectrometry (M):  
calculated 3072.4.

#### EXAMPLE 149

##### 15 Preparation of Peptide having SEQ ID NO. 149

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Ala Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 149]

20

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
25 Inc.), cleaved from the resin, deprotected and purified in

a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3172.5.

#### EXAMPLE 150

10

#### Preparation of Peptide having SEQ ID NO. 150

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Ala Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 150]

15

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is

20

25



then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3115.5.

5

EXAMPLE 151Preparation of Peptide having SEQ ID NO. 151

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
10 Glu Glu Ala Val Arg Leu Naphthylala Ile Glu Trp Leu Lys  
Asn-NH<sub>2</sub> [SEQ. ID. NO. 151]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
15 acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
20 Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3266.4.

25

EXAMPLE 152Preparation of Peptide having SEQ ID NO. 152

5     Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
      Glu Glu Ala Val Arg Leu Naphthylala Ile Glu Phe Leu Lys  
      Asn-NH<sub>2</sub> [SEQ. ID. NO. 152]

      The above-identified amidated peptide is assembled on  
10    4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
      acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
      using Fmoc-protected amino acids (Applied Biosystems,  
      Inc.), cleaved from the resin, deprotected and purified in  
      a similar way to Example 100. Used in analysis are Solvent  
15    A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
      Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
      Solvent A over 30 minutes) of the lyophilized peptide is  
      then carried out to determine the retention time of the  
      product peptide. Electrospray Mass Spectrometry (M):  
20    calculated 3209.4.

EXAMPLE 153Preparation of Peptide having SEQ ID NO. 153

25

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Val Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 153]

5           The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
10       a similar way to Example 100. Used in analysis are Solvent  
A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
15       product peptide. Electrospray Mass Spectrometry (M):  
calculated 3200.6.

#### EXAMPLE 154

20           Preparation of Peptide having SEQ ID NO. 154

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Val Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 154]

25

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3143.5.

#### EXAMPLE 155

15

#### Preparation of Peptide having SEQ ID NO. 155

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe tButylgly Glu Trp Leu Lys Asn-  
NH<sub>2</sub> [SEQ. ID. NO. 155]

20

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems,

25

Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).

Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3216.5.

10

EXAMPLE 156Preparation of Peptide having SEQ ID NO. 156

15

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe tButylgly Glu Phe Leu Lys Asn-  
NH<sub>2</sub> [SEQ. ID. NO. 156]

20

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).

25

Analytical RP-HPLC (gradient 30% to 60% Solvent B in

Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3159.4.

5

EXAMPLE 157

Preparation of Peptide having SEQ ID NO. 157

10 Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Asp Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 157]

The above-identified amidated peptide is assembled on  
15 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 100. Used in analysis are Solvent  
20 A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
25 calculated 3200.6.

EXAMPLE 158Preparation of Peptide having SEQ ID NO. 158

5

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Asp Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 158]

10

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
15 a similar way to Example 100. Used in analysis are Solvent  
A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
20 product peptide. Electrospray Mass Spectrometry (M):  
calculated 3143.5.

EXAMPLE 159

25

Preparation of Peptide having SEQ ID NO. 159

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Ala Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 159]

5

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
10 Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 100. Used in analysis are Solvent  
A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
15 then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3099.5.

#### EXAMPLE 160

20

#### Preparation of Peptide having SEQ ID NO. 160

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Ala Leu Lys Asn-NH<sub>2</sub>  
25 [SEQ. ID. NO. 160]



The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3081.4.

15

EXAMPLE 161Preparation of Peptide having SEQ ID NO. 161

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Ala Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 161]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)

using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).

5 Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3172.5.

10

#### EXAMPLE 162

##### Preparation of Peptide having SEQ ID NO. 162

15 Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Ala Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 162]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
20 acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).

25 Analytical RP-HPLC (gradient 30% to 60% Solvent B in

Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3115.5.

5

/ EXAMPLE 163

Preparation of Peptide having SEQ ID NO. 163

10 Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Ala Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 163]

The above-identified amidated peptide is assembled on  
15 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 100. Used in analysis are Solvent  
20 A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
25 calculated 3157.5.

EXAMPLE 164Preparation of Peptide having SEQ ID NO. 164

5

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Ala Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 164]

10

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
15 a similar way to Example 100. Used in analysis are Solvent  
A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
20 product peptide. Electrospray Mass Spectrometry (M):  
calculated 3100.4.

EXAMPLE 165

25

Preparation of Peptide having SEQ ID NO. 165

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Ala-NH<sub>2</sub>  
[SEQ. ID. NO. 165]

5

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
10 Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 100. Used in analysis are Solvent  
A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
15 then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3171.6.

#### EXAMPLE 166

20

#### Preparation of Peptide having SEQ ID NO. 166

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Ala-NH<sub>2</sub>  
25 [SEQ. ID. NO. 166]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3114.5.

15

EXAMPLE 167Preparation of Peptide having SEQ ID NO. 167

Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly  
Pro Ser Ser Gly Ala Pro Pro Pro-NH<sub>2</sub> [SEQ. ID. NO. 167]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)

using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).

- 5 Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4033.5.

10

#### EXAMPLE 168

##### Preparation of Peptide having SEQ ID NO. 168

- His Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
15 Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly  
Pro Ser Ser Gly Ala Pro Pro Pro-NH<sub>2</sub> [SEQ. ID. NO. 168]

- The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
20 acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
25 Analytical RP-HPLC (gradient 30% to 60% Solvent B in

Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3984.4.

5

EXAMPLE 169

Preparation of Peptide having SEQ ID NO. 169

10 His Gly Glu Ala Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly  
Pro Ser Ser Gly Ala Pro Pro-NH<sub>2</sub> [SEQ. ID. NO. 169]

The above-identified amidated peptide is assembled on  
15 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 100. Used in analysis are Solvent  
20 A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
25 calculated 4016.5.



EXAMPLE 170Preparation of Peptide having SEQ ID NO. 170

5

His Gly Glu Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly  
Pro Ser Ser Gly Ala Pro-NH<sub>2</sub> [SEQ. ID. NO. 170]

10

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
15 a similar way to Example 100. Used in analysis are Solvent  
A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
20 product peptide. Electrospray Mass Spectrometry (M):  
calculated 3861.3.

EXAMPLE 171

25

Preparation of Peptide having SEQ ID NO. 171

Ala Gly Glu Gly Thr Phe Thr Ser Asp Ala Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly  
Pro Ser Ser Gly Ala Pro-NH<sub>2</sub> [SEQ. ID. NO. 171]

5

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
10 Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 100. Used in analysis are Solvent  
A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
15 then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3746.1.

#### EXAMPLE 172

20

#### Preparation of Peptide having SEQ ID NO. 172

Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly  
25 Pro Ser Ser Gly Ala-NH<sub>2</sub> [SEQ. ID. NO. 172]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
5 using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 100. Used in analysis are Solvent  
A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
10 Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3742.1.

15

EXAMPLE 173Preparation of Peptide having SEQ ID NO. 173

His Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
20 Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly  
Pro Ser Ser Gly Ala-NH<sub>2</sub> [SEQ. ID. NO. 173]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
25 acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)

using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).

5 Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3693.1.

10

#### EXAMPLE 174

##### Preparation of Peptide having SEQ ID NO. 174

15 His Gly Glu Ala Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly  
Pro Ser Ser Gly-NH<sub>2</sub> [SEQ. ID. NO. 174]

20 The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent  
25 A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).

Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M):  
5 calculated 3751.2.

#### EXAMPLE 175

##### Preparation of Peptide having SEQ ID NO. 175

10

His Gly Glu Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly  
Pro Ser Ser-NH<sub>2</sub> [SEQ. ID. NO. 175]

15

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in  
20 a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the  
25 product peptide. Electrospray Mass Spectrometry (M):

calculated 3634.1.

EXAMPLE 176

5                   Preparation of Peptide having SEQ ID NO. 176

Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly  
Pro Ser-NH<sub>2</sub> [SEQ. ID. NO. 176]

10

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
15 Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 100. Used in analysis are Solvent  
A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
20 then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3526.9.

EXAMPLE 177

25

Preparation of Peptide having SEQ ID NO. 177

His Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly  
5 Pro Ser-NH<sub>2</sub> [SEQ. ID. NO. 177]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
10 using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 100. Used in analysis are Solvent  
A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
15 Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3477.9.

20

EXAMPLE 178Preparation of Peptide having SEQ ID NO. 178

His Gly Glu Ala Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
25 Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly

Pro-NH<sub>2</sub> [SEQ. ID. NO. 178]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
5 acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 100. Used in analysis are Solvent  
A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
10 Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3519.9.

15

EXAMPLE 179

Preparation of Peptide having SEQ ID NO. 179

20 His Gly Glu Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly  
Gly-NH<sub>2</sub> [SEQ. ID. NO. 179]

The above-identified amidated peptide is assembled on  
25 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy



acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3307.7.

#### EXAMPLE 180

##### Preparation of Peptide having SEQ ID NO. 180

Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly-NH<sub>2</sub>  
[SEQ. ID. NO. 180]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent

A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
5 product peptide. Electrospray Mass Spectrometry (M):  
calculated 3186.5.

#### EXAMPLE 181

#### 10 Preparation of Peptide having SEQ ID NO. 181

His Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly  
tPro Ser Ser Gly Ala tPro tPro tPro-NH<sub>2</sub> [SEQ. ID. NO. 181]

15

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
20 Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 100. Double couplings are required  
at residues 37,36 and 31. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
25 Solvent A over 30 minutes) of the lyophilized peptide is

then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4121.1.

5

EXAMPLE 182Preparation of Peptide having SEQ ID NO. 182

His Gly Glu Ala Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly  
10 Pro Ser Ser Gly Ala tPro tPro tPro-NH<sub>2</sub> [SEQ. ID. NO. 182].

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Double couplings are required at residues 37, 36 and 31. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
15  
20 Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4173.2.

25

EXAMPLE 183Preparation of Peptide having SEQ ID NO. 183

5 His Gly Glu Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly  
NMeala Ser Ser Gly Ala NMeala NMeala-NH<sub>2</sub> [SEQ. ID. NO. 183]

The above-identified amidated peptide is assembled on  
10 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Compound 1. Double couplings are required  
15 at residues 36 and 31. Used in analysis are Solvent A (0.1%  
TFA in water) and Solvent B (0.1% TFA in ACN). Analytical  
RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30  
minutes) of the lyophilized peptide is then carried out to  
determine the retention time of the product peptide.  
20 Electrospray Mass Spectrometry (M): calculated 3796.1.

EXAMPLE 184Preparation of Peptide having SEQ ID NO. 184

25

Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly  
hPro Ser Ser Gly Ala hPro-NH<sub>2</sub> [SEQ. ID. NO. 184]

5           The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
10       a similar way to Example 100. A double coupling is required  
at residue 31. Used in analysis are Solvent A (0.1% TFA in  
water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC  
(gradient 30% to 60% Solvent B in Solvent A over 30  
minutes) of the lyophilized peptide is then carried out to  
15       determine the retention time of the product peptide.  
Electrospray Mass Spectrometry (M): calculated 3871.1.

#### EXAMPLE 185

20           Preparation of Peptide having SEQ ID NO. 185

His Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly  
Pro Ser Ser Gly Ala-NH<sub>2</sub> [SEQ. ID. NO. 185]

25

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3750.2.

#### EXAMPLE 186

15

#### Preparation of Peptide having SEQ ID NO. 186

His Gly Asp Ala Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly  
Gly-NH<sub>2</sub> [SEQ. ID. NO. 186]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems,

Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).

Analytical RP-HPLC (gradient 30% to 60% Solvent B in

5 Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3408.8.

10

EXAMPLE 187Preparation of Peptide having SEQ ID NO. 187

Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu  
15 Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly  
Pro Ser Ser Gly Ala Pro Pro Pro Ser-NH<sub>2</sub> [SEQ. ID. NO. 187]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
20 acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 100. Used in analysis are Solvent  
A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
25 Analytical RP-HPLC (gradient 30% to 60% Solvent B in

Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4120.6.

5

EXAMPLE 188

Preparation of Peptide having SEQ ID NO. 188

10 Ala Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu  
Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly  
Pro Ser Ser Gly Ala Pro Pro Pro Ser-NH<sub>2</sub> [SEQ. ID. NO. 188]

The above-identified amidated peptide is assembled on  
15 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g)  
using Fmoc-protected amino acids (Applied Biosystems,  
Inc.), cleaved from the resin, deprotected and purified in  
a similar way to Example 100. Used in analysis are Solvent  
20 A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
25 calculated 4005.5.



EXAMPLE 189

Preparation of C-terminal carboxylic acid peptides  
5 corresponding to the above C-terminal amide sequences for  
Peptides having SEQ ID NOS. 100-166, 172-177, 179-180 and  
185-188.

C-terminal carboxylic acid peptides corresponding to  
10 amidated having SEQ ID NOS. 100-166, 172-177, 179-180 and  
185-188 are assembled on the so called Wang resin (p-  
alkoxybenzylalcohol resin (Bachem, 0.54 mmole/g)) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
15 similar way to that described in Example 100. Used in  
analysis are Solvent A (0.1% TFA in water) and Solvent B  
(0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60%  
Solvent B in Solvent A over 30 minutes) of the lyophilized  
peptide is then carried out to determine the retention time  
20 of the product peptide. Electrospray Mass Spectrometry  
provides an experimentally determined (M).

EXAMPLE 190

25

Preparation of C-terminal carboxylic acid peptides  
corresponding to the above C-terminal amide sequences for  
Peptides having SEQ ID NOS. 167-171, 178 and 181-184.

5           C-terminal carboxylic acid peptides corresponding to  
amidated SEQ ID NOS. 167-171, 178 and 181-184 are assembled  
on the 2-chlorotritylchloride resin (200-400 mesh), 2% DVB  
(Novabiochem, 0.4-1.0 mmole/g)) using Fmoc-protected amino  
acids (Applied Biosystems, Inc.), cleaved from the resin,  
10       deprotected and purified in a similar way to that described  
in Example 100. Used in analysis are Solvent A (0.1% TFA in  
water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC  
(gradient 30% to 60% Solvent B in Solvent A over 30  
minutes) of the lyophilized peptide is then carried out to  
15       determine the retention time of the product peptide.  
Electrospray Mass Spectrometry provides an experimentally  
determined (M).

20           Various modifications of the invention in addition to  
those shown and described herein will become apparent to  
those skilled in the art from the foregoing description and  
fall within the scope of the following claims.

WE CLAIM:

1. A method for treating conditions or disorders which can be alleviated by reducing food intake in a subject comprising administering to said subject a therapeutically effective amount of an exendin or an exendin agonist.

2. The method according to claim 1 wherein said exendin or exendin agonist is administered parenterally.

3. The method according to claim 2 wherein said parenteral administration is by injection.

4. The method according to claim 3 wherein the injection is a peripheral injection.

5. The method according to claim 1 wherein about 10  $\mu$ g-30 $\mu$ g to about 5mg of the exendin or exendin agonist is administered per day.

6. The method according to claim 1 wherein about 10  $\mu$ g-30  $\mu$ g to about 2 mg of the exendin or exendin agonist is administered per day.

7. The method according to claim 1, wherein about 30  $\mu$ g to about 500  $\mu$ g of the exendin or exendin agonist is administered per day.

8. The method of claim 1 wherein said condition or disorder is obesity.

9. The method of claim 1 wherein said condition or disorder is Type II diabetes.

10. The method of claim 1 wherein said subject is

human.

11. The method of claim 1 wherein said condition or disorder is an eating disorder.

12. The method of claim 1 wherein said condition or disorder is insulin-resistance syndrome.

13. A method for reducing the appetite of a subject comprising administering to said subject an appetite-lowering amount of an exendin or an exendin agonist.

14. A method for reducing the weight of a subject comprising administering to said subject a therapeutically effective amount of an exendin or an exendin agonist.

15. A method for lowering plasma lipids comprising administering to said subject a therapeutically effective amount of an exendin or an exendin agonist.

16. The method according to any of claims 1-15 wherein said exendin is exendin-3.

17. The method according to any of claims 1-15 wherein said exendin is exendin-4.

18. The method according to any of claims 1-15 wherein said exendin agonist is selected from the group consisting of exendin-4 (1-30), exendin-4 (1-30) amide, exendin-4 (1-28) amide, <sup>14</sup>Leu,<sup>25</sup>Phe exendin-4 amide, <sup>14</sup>Leu,<sup>25</sup>Phe exendin-4 (1-28) amide, and <sup>14</sup>Leu,<sup>22</sup>Ala,<sup>25</sup>Phe exendin-4 (1-28) amide.

19. The method according to any of claims 1-15, further comprising administering a therapeutically effective

amount of one or more compounds selected from the group consisting essential of an amylin agonist, a leptin, and a CCK.

20. The method according to any of claims 1-15 wherein  
5 said exendin agonist is an exendin agonist according to Formula I.

21. The method according to any of claims 1-15 wherein said exendin agonist is an exendin agonist according to Formula II.

10 22. The method according to any of claims 1-15 wherein said exendin agonist is an exendin agonist according to Formula III.

23. A pharmaceutical composition for use in the treatment of conditions or disorders associated with  
15 hypernutrition comprising a therapeutically effective amount of an exendin or exendin agonist in association with a pharmaceutically acceptable carrier.

24. The pharmaceutical composition according to claim 21, wherein said exendin is exendin-3.

20 25. The pharmaceutical composition according to claim 21 wherein said exendin is exendin-4.

26. The pharmaceutical composition according to claim 21 wherein said exendin agonist is selected from the group consisting of exendin-4 (1-30), exendin-4 (1-30) amide,  
25 exendin-4 (1-28) amide, <sup>14</sup>Leu, <sup>25</sup>Phe exendin-4 amide, <sup>14</sup>Leu, <sup>25</sup>Phe

exendin-4 (1-28) amide, and <sup>14</sup>Leu, <sup>22</sup>Ala, <sup>25</sup>Phe exendin-4 (1-28) amide.

27. The pharmaceutical composition of claim 21 wherein said therapeutically effective amount is a therapeutically effective amount for a human subject.

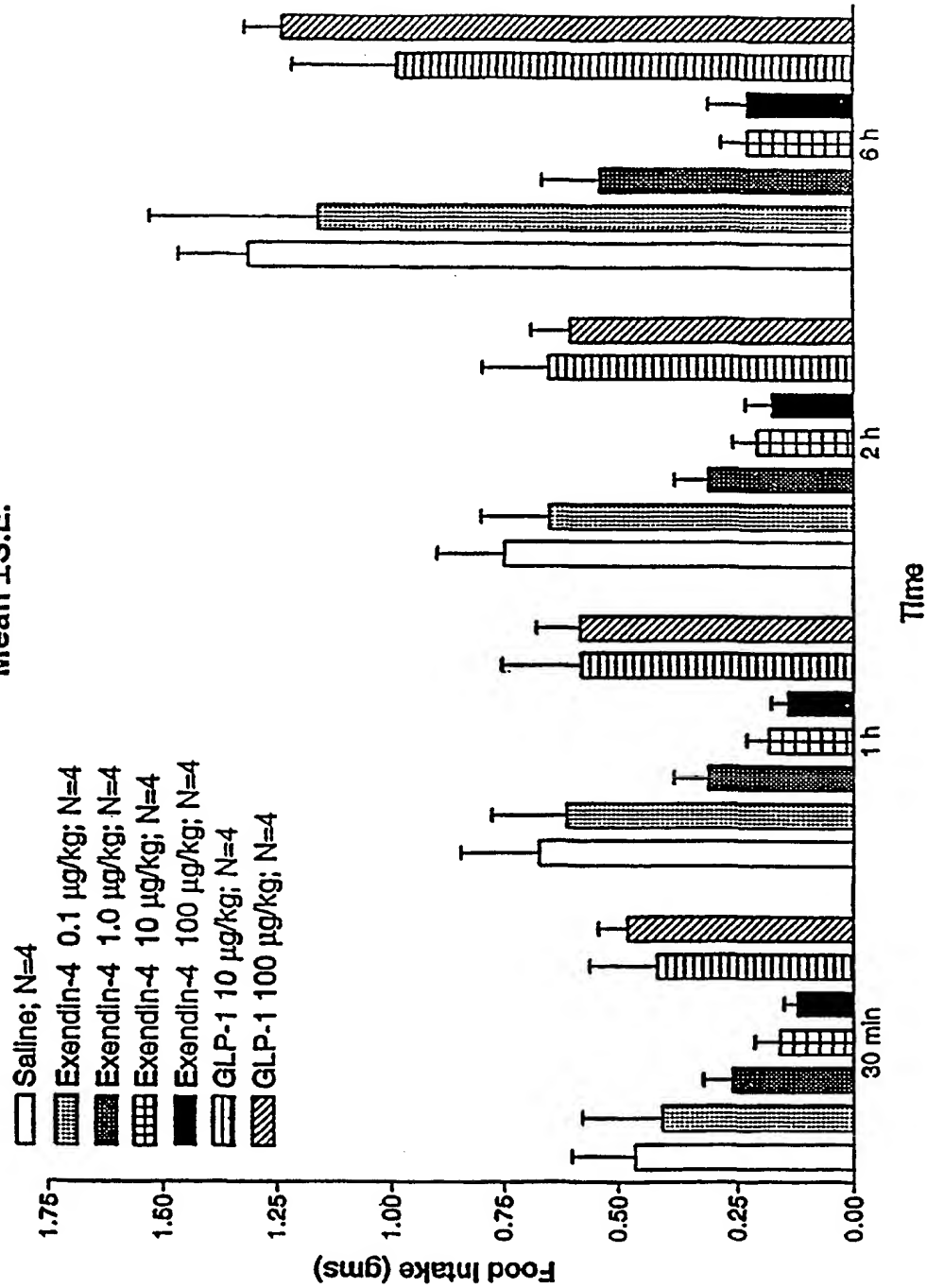
28. A pharmaceutical composition for use in reducing the appetite of a subject comprising a therapeutically effective amount of an exendin or exendin agonist in association with a pharmaceutically acceptable carrier.

29. A pharmaceutical composition for use in reducing the weight of a subject comprising a therapeutically effective amount of an exendin or exendin agonist in association with a pharmaceutically acceptable carrier.

30. A pharmaceutical composition for use in lowering the plasma lipid level of a subject comprising a therapeutically effective amount of an exendin or exendin agonist in association with a pharmaceutically acceptable carrier.

31. The pharmaceutical composition according to any of claims 21-28, further comprising a therapeutically effective amount of one or more compounds selected from the group consisting essentially of an amylin agonist, a leptin, and a CCK.

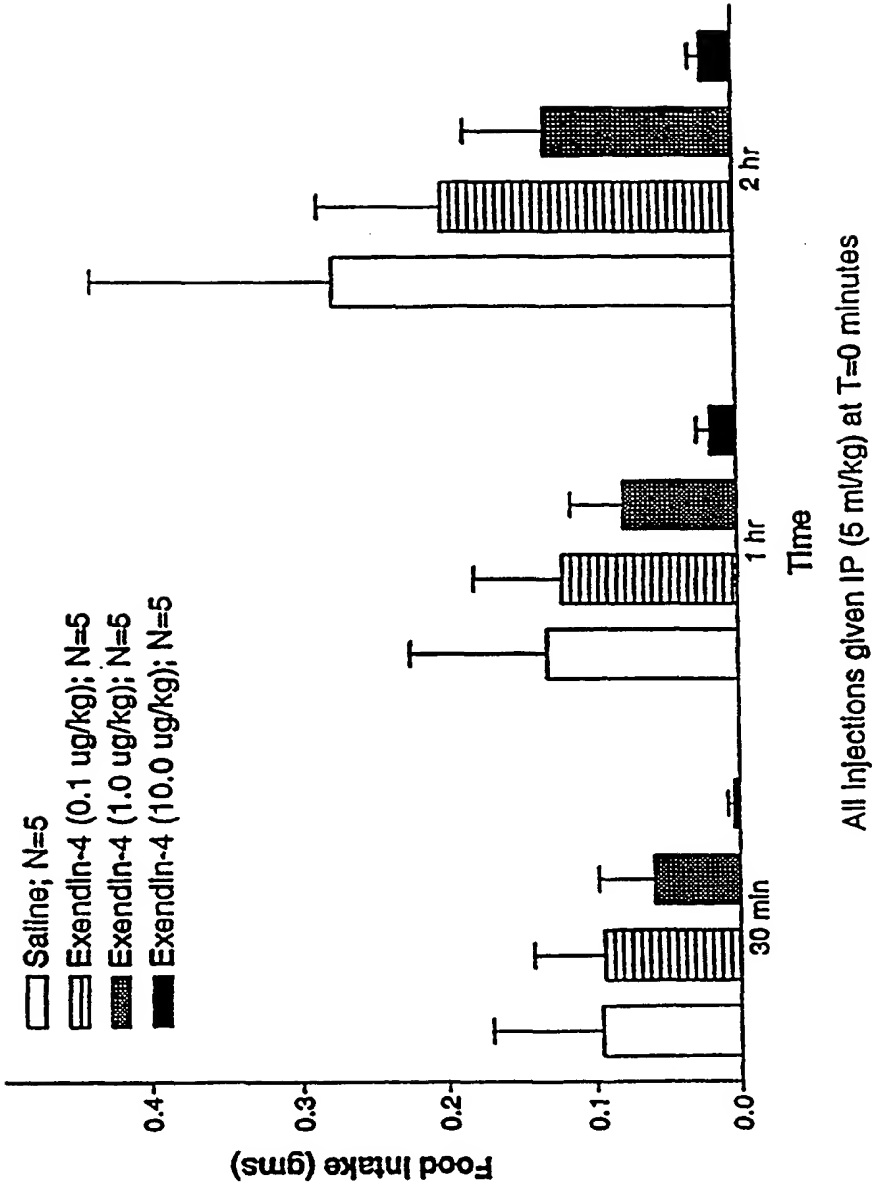
# Effect of Exendin-4 and GLP-1 on Food Intake in NIH/SW Mice Mean $\pm$ S.E.



All injections given IP (5 ml/kg) at T=0 minutes

FIGURE 1

Effect of Exendin-4 on Food Intake in  
Female ob/ob Mice  
Mean  $\pm$  S.E.

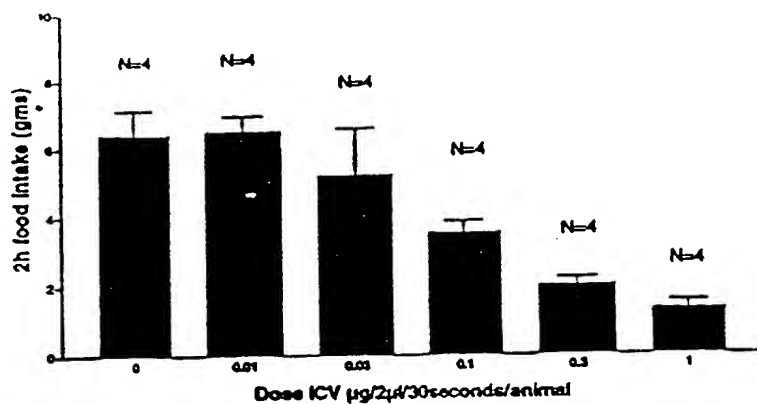


All Injections given IP (5 ml/kg) at T=0 minutes

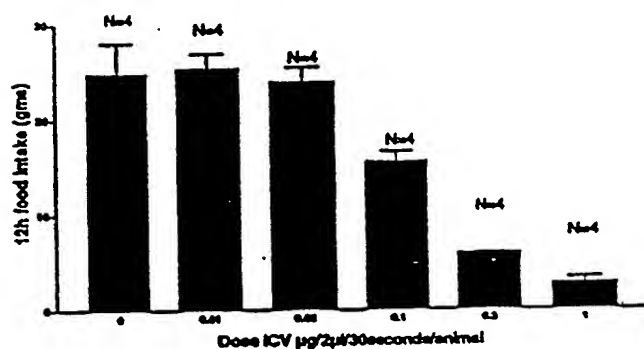
FIGURE 2



in HSD rats during the onset of dark cycle



Effect of ICV Exendin-4 on food intake  
in HSD rats during the onset of dark cycle



Effect of ICV Exendin-4 on food intake  
in HSD rats during the onset of dark cycle

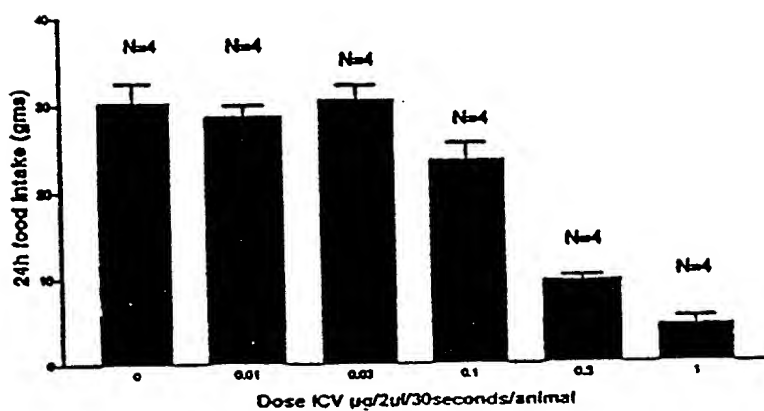
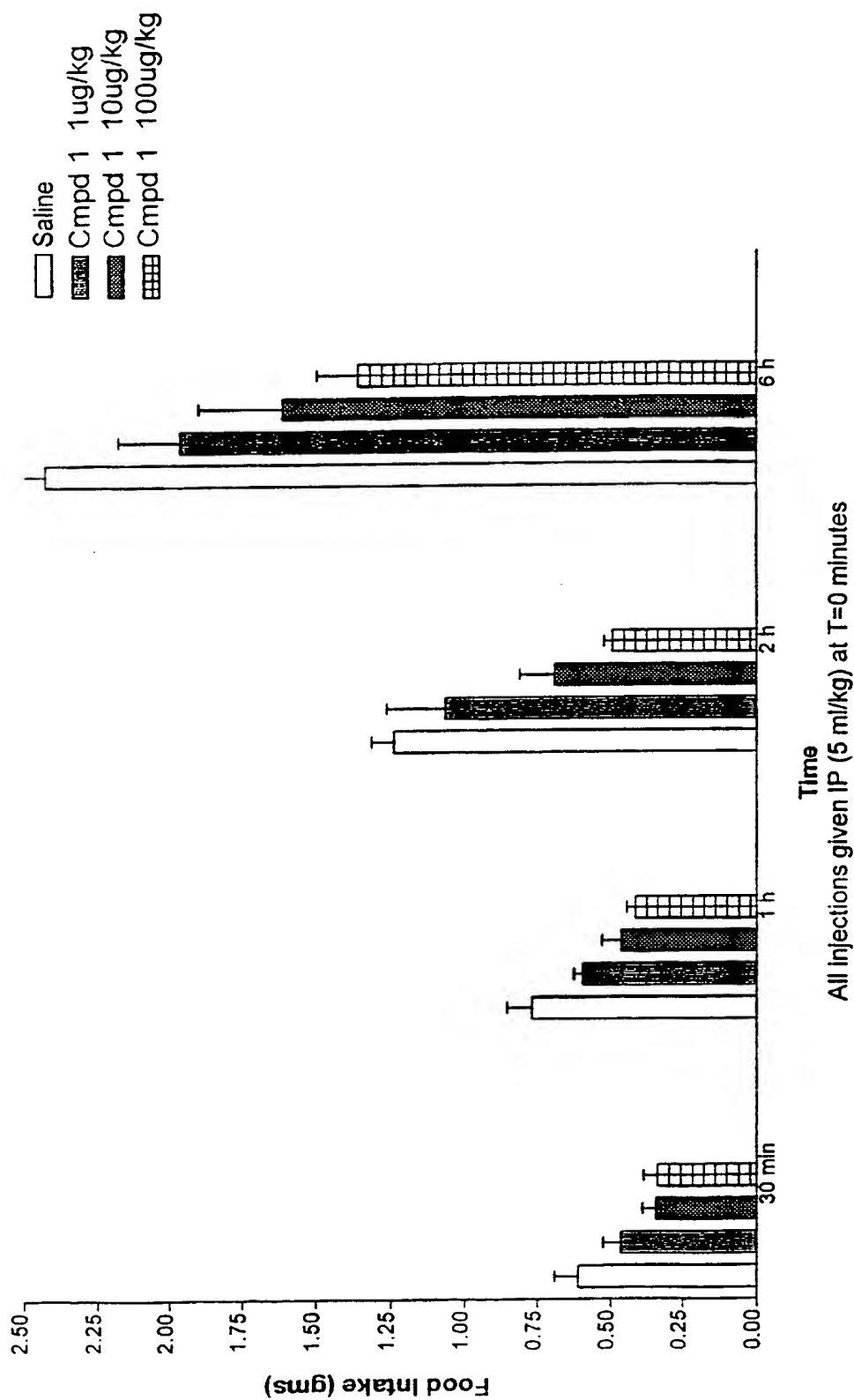


FIGURE 3

**Effect of Compound 1 on Food Intake  
in NIH/SW Mice  
Mean  $\pm$  S.E.**



**FIGURE 4**

Effect of Compound 2 on Food Intake  
in NIH/SW Mice

Mean  $\pm$  S.E.

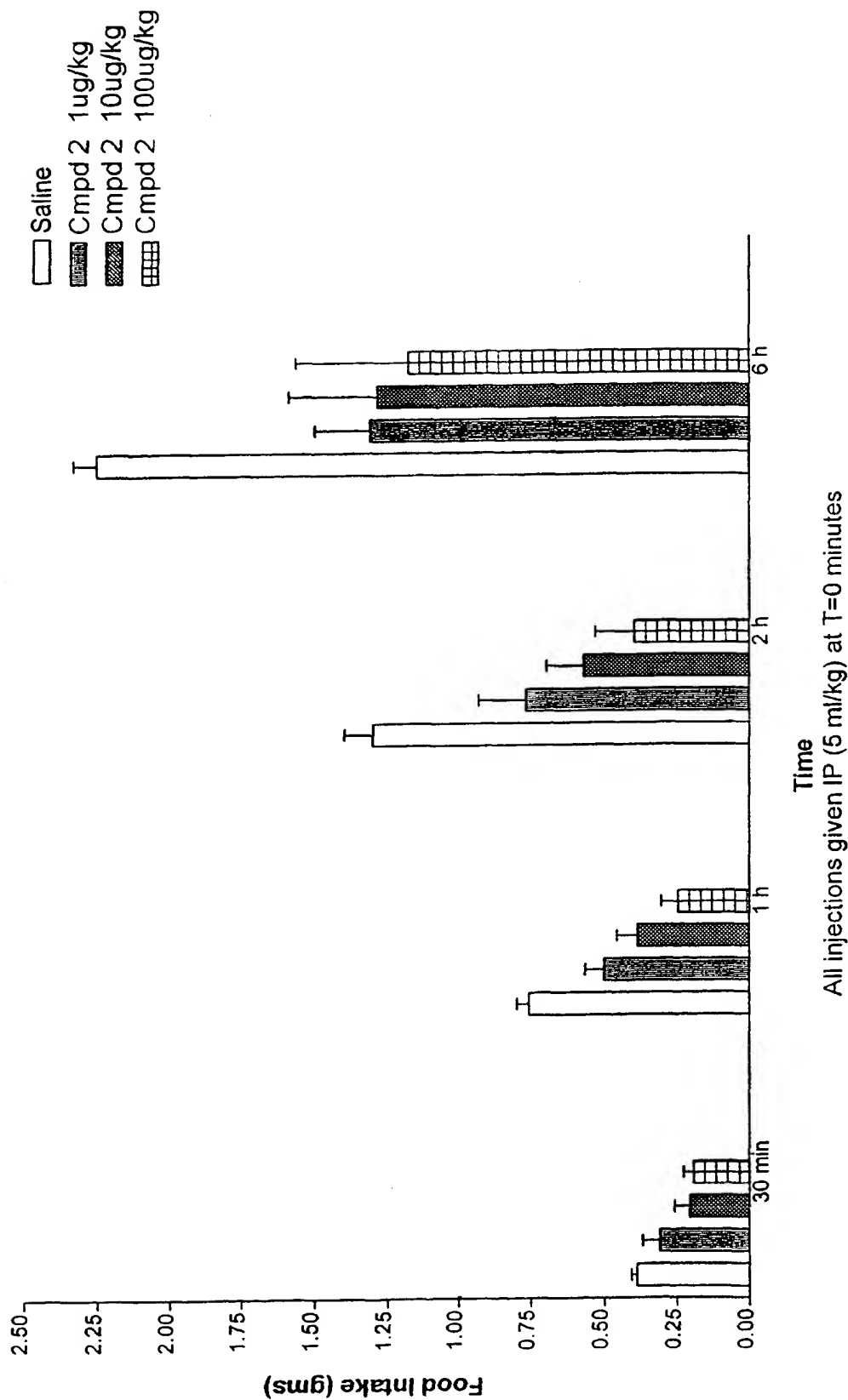
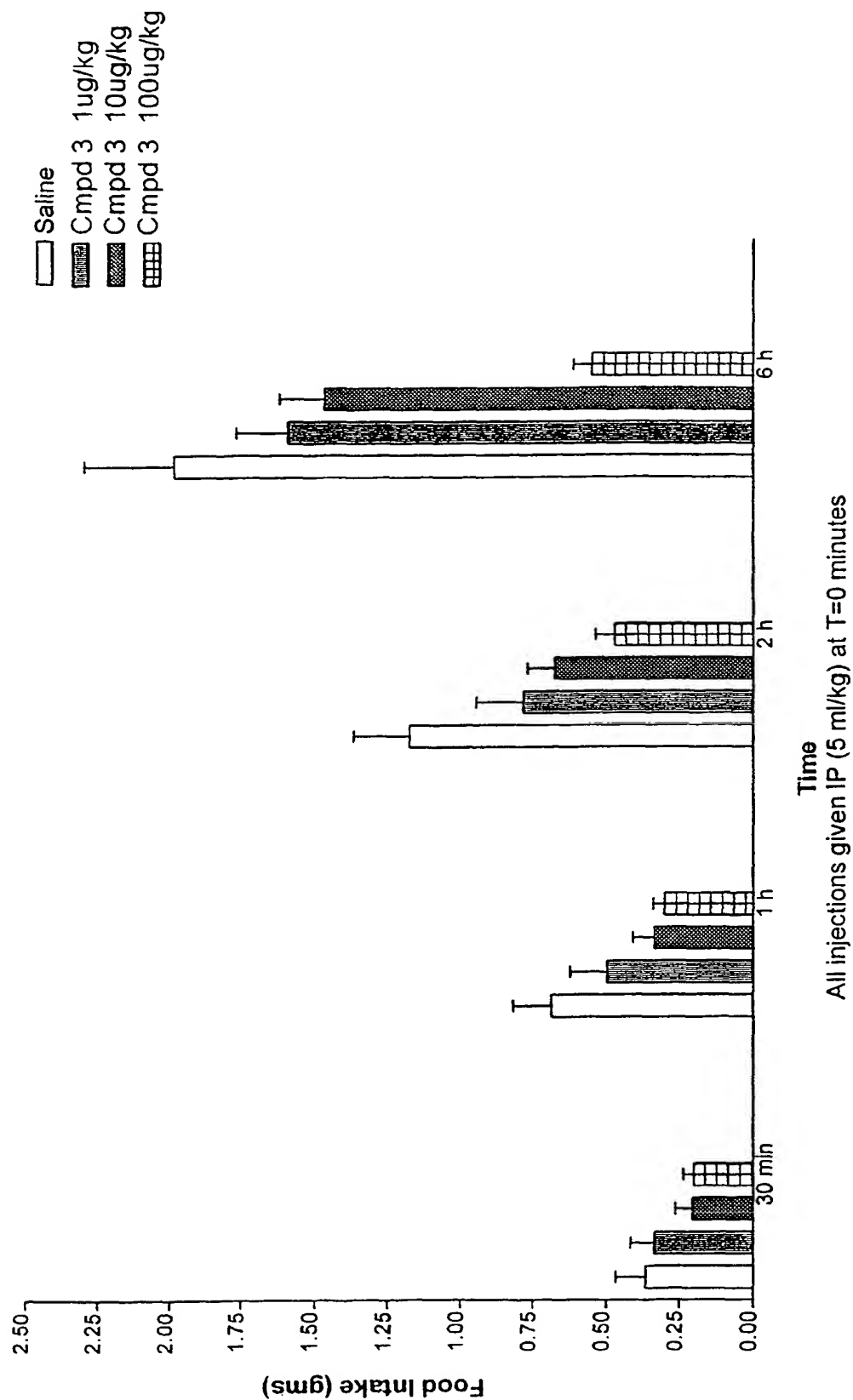


FIGURE 5

**Effect of Compound 3 on Food Intake  
in NIH/SW Mice  
Mean  $\pm$  S.E.**



**FIGURE 6**

Effect of Compound 4 on Food Intake  
in NIH/SW Mice  
Mean  $\pm$  S.E.

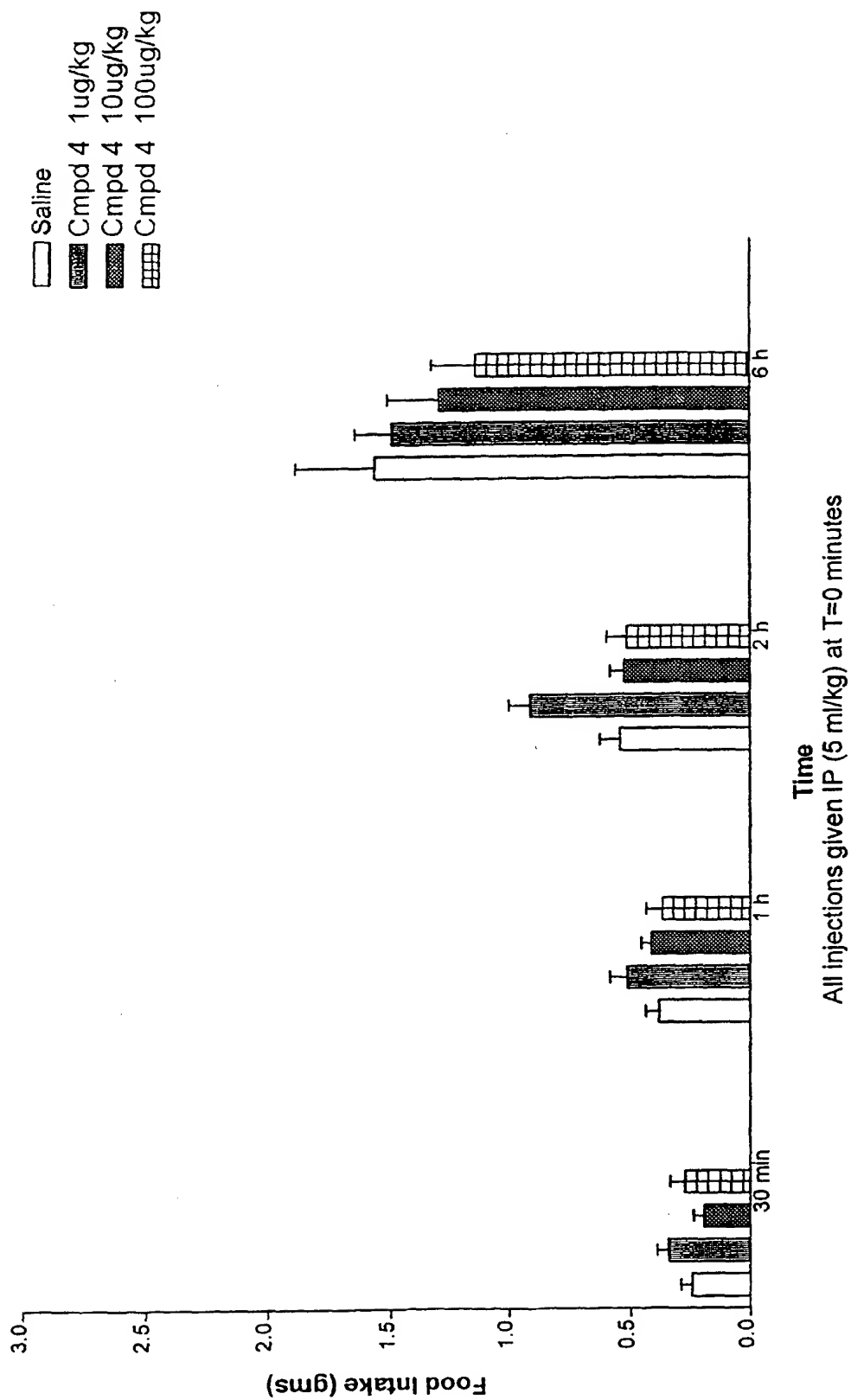
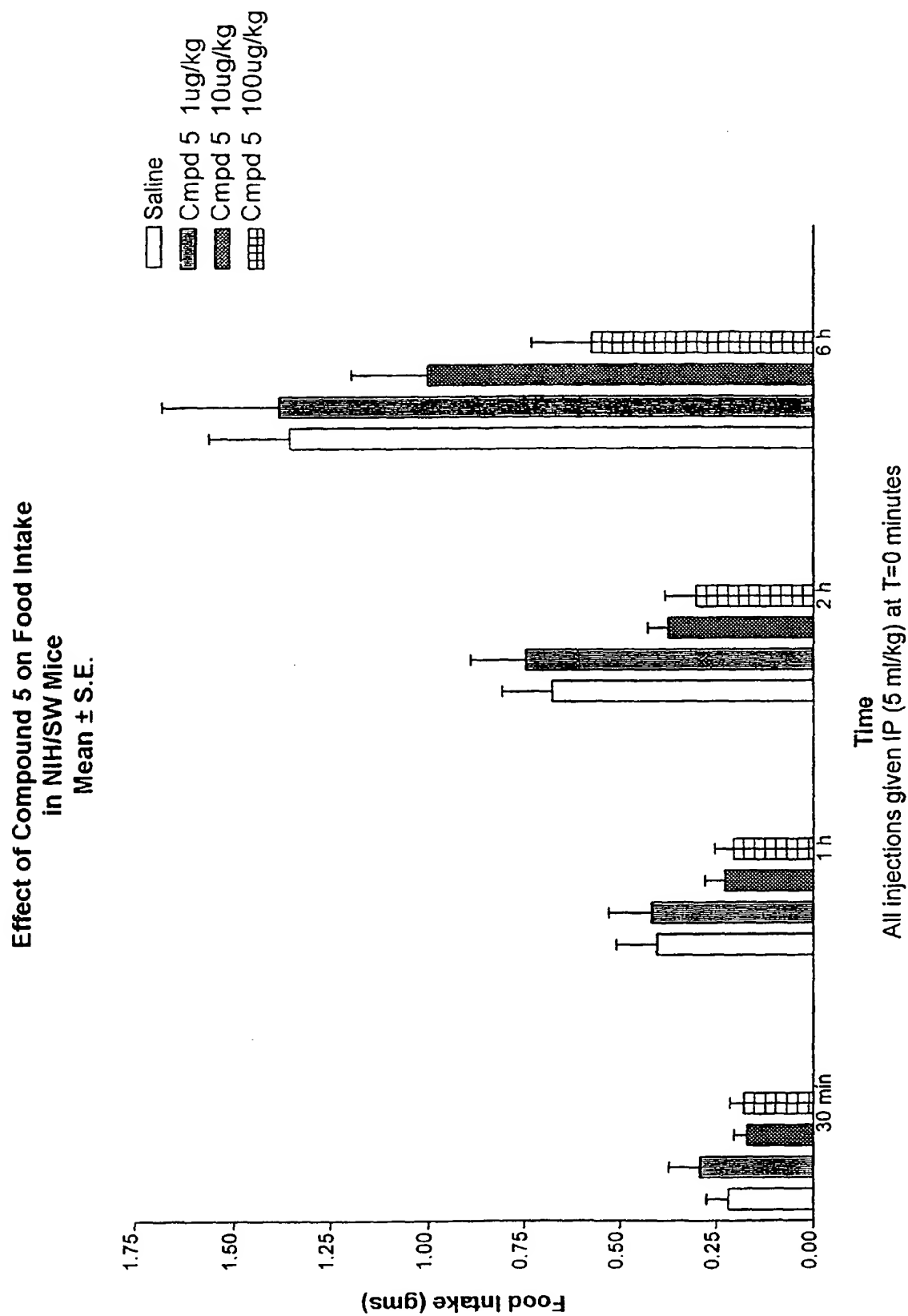


FIGURE 7



**FIGURE 8**

Effect of Compound 6 on Food Intake  
in NIH/SW Mice  
Mean  $\pm$  S.E.

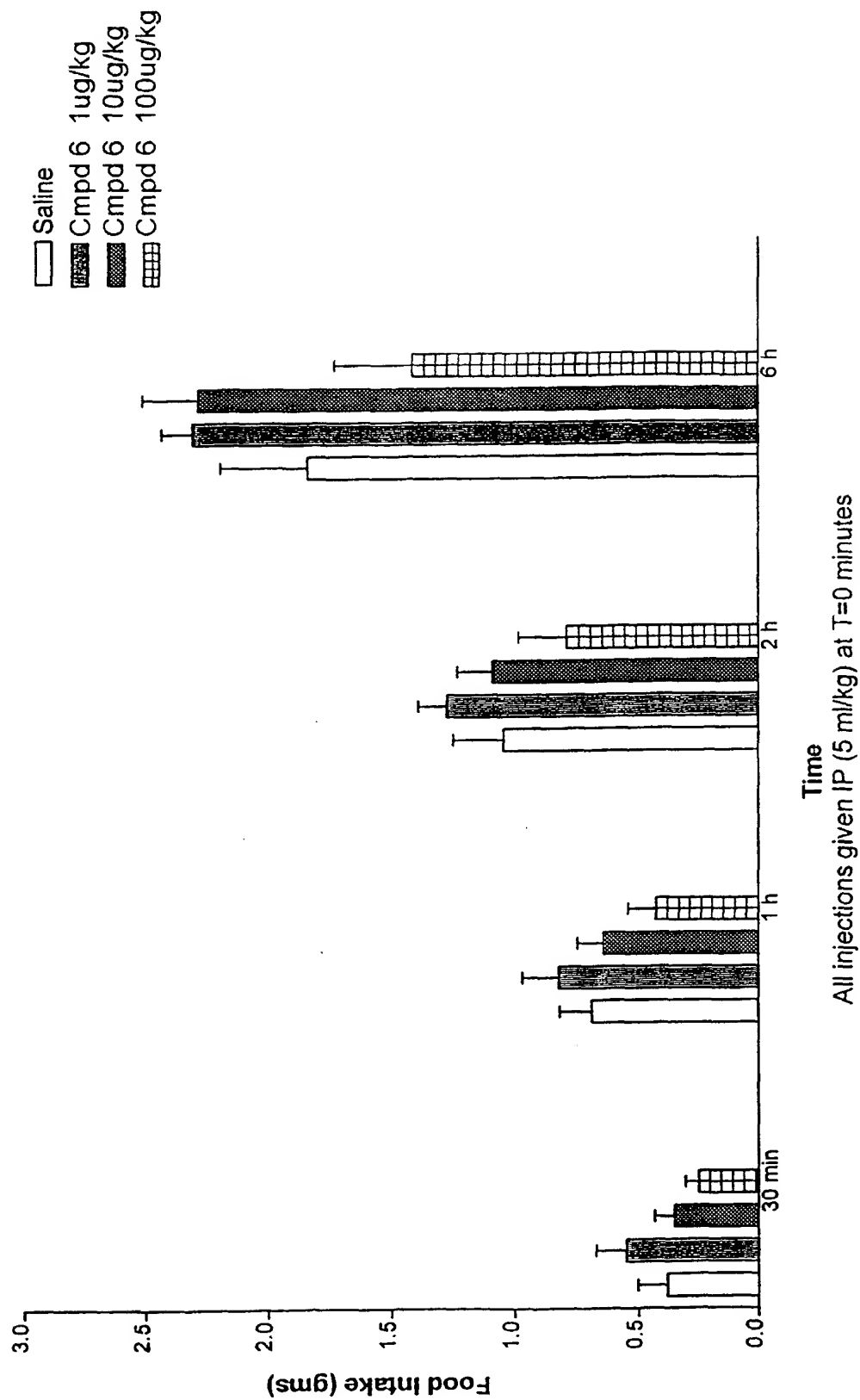


FIGURE 9

1 Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Gly Thr Xaa<sub>4</sub> Xaa<sub>5</sub> Xaa<sub>6</sub> Xaa<sub>7</sub> Ser Lys Gln Xaa<sub>8</sub> Glu Glu Glu Ala Val Arg Leu  
 5  
 10  
 15  
 20  
 25  
 30  
 35  
 Xaa<sub>10</sub> Xaa<sub>11</sub> Xaa<sub>12</sub> Xaa<sub>13</sub> Leu Lys Asn Gly Gly Xaa<sub>14</sub> Ser Ser Gly Ala Xaa<sub>15</sub> Xaa<sub>16</sub> Xaa<sub>17</sub> Xaa<sub>18</sub>-Z

[SEQ. ID. NO.]	Xaa <sub>1</sub>	Xaa <sub>2</sub>	Xaa <sub>3</sub>	Xaa <sub>4</sub>	Xaa <sub>5</sub>	Xaa <sub>6</sub>	Xaa <sub>7</sub>	Xaa <sub>8</sub>	Xaa <sub>9</sub>	Xaa <sub>10</sub>	Xaa <sub>11</sub>	Xaa <sub>12</sub>	Xaa <sub>13</sub>	Xaa <sub>14</sub>	Xaa <sub>15</sub>	Xaa <sub>16</sub>	Xaa <sub>17</sub>	Xaa <sub>18</sub>	Z
9	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Leu	Phe	Ile	Glu	Phe	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
10	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Leu	Phe	Ile	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
11	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	Ile	Glu	Phe	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
12	Tyr	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	Ile	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
13	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	Ile	Glu	Trp	Pro	Pro	Pro	Pro	Tyr	NH <sub>2</sub>
14	His	Gly	Asp	Phe	Thr	Ser	Asp	Leu	Met	Phe	Ile	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
15	His	Gly	Glu	naph	Thr	Ser	Asp	Leu	Met	Phe	Ile	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
16	His	Gly	Glu	Phe	Ser	Ser	Asp	Leu	Met	Phe	Ile	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
17	His	Gly	Glu	Phe	Ser	Thr	Asp	Leu	Met	Phe	Ile	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
18	His	Gly	Glu	Phe	Thr	Thr	Asp	Leu	Met	Phe	Ile	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
19	His	Gly	Glu	Phe	Thr	Ser	Glu	Leu	Met	Phe	Ile	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
20	His	Gly	Glu	Phe	Thr	Ser	Asp	pGly	Met	Phe	Ile	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
21	His	Gly	Glu	Phe	Thr	Ser	Asp	pGly	Leu	Phe	Ile	Glu	Phe	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
22	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	pGly	Phe	Ile	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>

**FIGURE 10**  
(Sheet 1 of 2)



[SEQ. ID. NO.]	Xaa <sub>1</sub>	Xaa <sub>2</sub>	Xaa <sub>3</sub>	Xaa <sub>4</sub>	Xaa <sub>5</sub>	Xaa <sub>6</sub>	Xaa <sub>7</sub>	Xaa <sub>8</sub>	Xaa <sub>9</sub>	Xaa <sub>10</sub>	Xaa <sub>11</sub>	Xaa <sub>12</sub>	Xaa <sub>13</sub>	Xaa <sub>14</sub>	Xaa <sub>15</sub>	Xaa <sub>16</sub>	Xaa <sub>17</sub>	Xaa <sub>18</sub>	Z
23	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	pGly	Phe	Ile	Glu	Phe	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
24	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	naph	Ile	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
25	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	Val	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
26	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Leu	Phe	Val	Glu	Phe	Pro	Pro	Pro	Pro	Ser	NH
27	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	tBuG	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
28	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Leu	Phe	tBuG	Glu	Phe	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
29	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	Ile	Asp	Trp	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
30	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	Ile	Glu	Phe	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
31	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	Ile	Glu	Trp	tPro	tPro	tPro	tPro	Ser	NH <sub>2</sub>
32	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	Ile	Glu	Trp	Pro	tPro	tPro	tPro	Ser	NH <sub>2</sub>
33	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	Ile	Glu	Trp	hPro	hPro	hPro	hPro	Ser	NH <sub>2</sub>
34	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	Ile	Glu	Trp	Pro	hPro	hPro	hPro	Ser	NH <sub>2</sub>
35	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Leu	Phe	Ile	Glu	Phe	tPro	tPro	tPro	tPro	Ser	NH <sub>2</sub>
36	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Leu	Phe	Ile	Glu	Phe	hPro	hPro	hPro	hPro	Ser	NH <sub>2</sub>
37	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	Ile	Glu	Trp	MeAla	MeAla	MeAla	MeAla	Ser	NH
38	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	Ile	Glu	Trp	Pro	MeAla	MeAla	MeAla	Ser	NH
39	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Leu	Phe	Ile	Glu	Phe	MeAla	MeAla	MeAla	MeAla	Ser	NH

**FIGURE 10**  
(Sheet 2 of 2)

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/00449

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 38/16

US CL : 514/2, 866

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/2, 866

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
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CAS ONLINE, MEDLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,424,286 A (ENG) 13 June 1995 see entire document.	1-31

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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Date of mailing of the international search report

29 MAY 1998

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Form PCT/ISA/210 (second sheet)(July 1992)\*



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification <sup>6</sup> : <b>A61K 38/16</b></p>	<p><b>A1</b></p>	<p>(11) International Publication Number: <b>WO 98/30231</b> (43) International Publication Date: 16 July 1998 (16.07.98)</p>												
<p>(21) International Application Number: PCT/US98/00449 (22) International Filing Date: 7 January 1998 (07.01.98) (30) Priority Data:  <table border="0"> <tr> <td>60/034,905</td> <td>7 January 1997 (07.01.97)</td> <td>US</td> </tr> <tr> <td>60/055,404</td> <td>8 August 1997 (08.08.97)</td> <td>US</td> </tr> <tr> <td>60/066,029</td> <td>14 November 1997 (14.11.97)</td> <td>US</td> </tr> <tr> <td>60/065,442</td> <td>14 November 1997 (14.11.97)</td> <td>US</td> </tr> </table> <p>(71) Applicant: AMYLIN PHARMACEUTICALS, INC. [US/US]; 9373 Towne Centre Drive, San Diego, CA 92121 (US). (72) Inventors: BEELEY, Nigel, Robert, Arnold; 227 Loma Corta Drive, Solana Beach, CA 92075 (US). PRICKETT, Kathryn, S.; 7612 Trailbrush Terrace, San Diego, CA 92126 (US). BHAVSAR, Sunil; Apartment #7, 917 Torrance Street, San Diego, CA 92103 (US). (74) Agents: DUFT, Bradford, J. et al.; Lyon &amp; Lyon LLP, First Interstate World Center, Suite 4700, 633 West Fifth Street, Los Angeles, CA 90071 (US).</p> </p>		60/034,905	7 January 1997 (07.01.97)	US	60/055,404	8 August 1997 (08.08.97)	US	60/066,029	14 November 1997 (14.11.97)	US	60/065,442	14 November 1997 (14.11.97)	US	<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
60/034,905	7 January 1997 (07.01.97)	US												
60/055,404	8 August 1997 (08.08.97)	US												
60/066,029	14 November 1997 (14.11.97)	US												
60/065,442	14 November 1997 (14.11.97)	US												
<p>(54) Title: USE OF EXENDINS AND AGONISTS THEREOF FOR THE REDUCTION OF FOOD INTAKE (57) Abstract   <p>Methods for treating conditions or disorders which can be alleviated by reducing food intake are disclosed which comprise administration of an effective amount of an exendin or an exendin agonist, alone or in conjunction with other compounds or compositions that effect satiety. The methods are useful for treating conditions or disorders, including obesity, Type II diabetes, eating disorders, and insulin-resistance syndrome. The methods are also useful for lowering the plasma glucose level, lowering the plasma lipid level, reducing the cardiac risk, reducing the appetite, and reducing the weight of subjects. Pharmaceutical compositions for use in the methods of the invention are also disclosed.</p> </p>														

\*(Referred to in PCT Gazette No. 45/1998, Section II)

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EE	Estonia	LR	Liberia	SG	Singapore		

USE OF EXENDINS AND AGONISTS THEREOF  
FOR THE REDUCTION OF FOOD INTAKE

5 This application claims the benefit of U.S.  
Provisional Application No. 60/034,905, filed January 7,  
1997, U.S. Provisional Application No. 60/055,404, filed  
August 8, 1997, U.S. Provisional Application No.  
60/066,029 filed November 14, 1997, and U.S. Provisional  
Application No. 60/065,442, November 14, 1997.

10

FIELD OF THE INVENTION

The present invention relates to methods for treating  
conditions or disorders which can be alleviated by  
reducing food intake comprising administration of an  
15 effective amount of an exendin or an exendin agonist alone  
or in conjunction with other compounds or compositions  
that affect satiety such as a leptin or an amylin agonist.  
The methods are useful for treating conditions or  
disorders, in which the reduction of food intake is of  
20 value, including obesity, Type II diabetes, eating  
disorders, and insulin-resistance syndrome. The methods  
are also useful for lowering the plasma lipid level,  
reducing the cardiac risk, reducing the appetite, and  
reducing the weight of subjects. Pharmaceutical  
25 compositions for use in the methods of the invention are  
also disclosed.

### BACKGROUND

The following description summarizes information relevant to the present invention. It is not an admission that any of the information provided herein is prior art to the presently claimed invention, nor that any of the publications specifically or implicitly referenced are prior art to that invention.

### Exendin

Exendins are peptides that are found in the venom of the Gila-monster, a lizard found in Arizona, and the Mexican Beaded Lizard. Exendin-3 is present in the venom of Heloderma horridum, and exendin-4 is present in the venom of Heloderma suspectum (Eng, J., et al., J. Biol. Chem., 265:20259-62, 1990; Eng, J., et al., J. Biol. Chem., 267:7402-05, 1992). The exendins have some sequence similarity to several members of the glucagon-like peptide family, with the highest homology, 53%, being to GLP-1[7-36]NH<sub>2</sub> (Goke, et al., J. Biol. Chem., 268:19650-55, 1993). GLP-1[7-36]NH<sub>2</sub>, also known as proglucagon[78-107], has an insulinotropic effect, stimulating insulin secretion from pancreatic  $\beta$ -cells; GLP also inhibits glucagon secretion from pancreatic  $\alpha$ -cells (Orskov, et al., Diabetes, 42:658-61, 1993; D'Alessio, et al., J. Clin. Invest., 97:133-38, 1996). GLP-1 is reported to inhibit gastric emptying (Williams B, et al., J. Clin. Endocrinol Metab 81 (1): 327-32, 1996; Wettergren A, et al., Dig Dis Sci 38 (4): 665-73, 1993), and gastric acid

secretion. (Schjoldager BT, et al., Dig Dis Sci 34 (5): 703-8, 1989; O'Halloran DJ, et al., J Endocrinol 126 (1): 169-73, 1990; Wettergren A, et al., Dig Dis Sci 38 (4): 665-73, 1993). GLP-1[7-37], which has an additional  
5 glycine residue at its carboxy terminus, also stimulates insulin secretion in humans (Orskov, et al., Diabetes, 42:658-61, 1993). A transmembrane G-protein adenylate-cyclase-coupled receptor believed to be responsible for the insulinotropic effect of GLP-1 is reported to have  
10 been cloned from a  $\beta$ -cell line (Thorens, Proc. Natl. Acad. Sci. USA 89:8641-45 (1992)).

Exendin-4 potently binds at GLP-1 receptors on insulin-secreting  $\beta$ TC1 cells, at dispersed acinar cells from guinea pig pancreas, and at parietal cells from  
15 stomach; the peptide is also said to stimulate somatostatin release and inhibit gastrin release in isolated stomachs (Goke, et al., J. Biol. Chem. 268:19650-55, 1993; Schepp, et al., Eur. J. Pharmacol., 69:183-91, 1994; Eissele, et al., Life Sci., 55:629-34, 1994).

20 Exendin-3 and exendin-4 were reported to stimulate cAMP production in, and amylase release from, pancreatic acinar cells (Malhotra, R., et al., Regulatory Peptides, 41:149-56, 1992; Raufman, et al., J. Biol. Chem. 267:21432-37, 1992; Singh, et al., Regul. Pept. 53:47-59, 1994). The  
25 use of exendin-3 and exendin-4 as insulinotropic agents for the treatment of diabetes mellitus and the prevention of hyperglycemia has been proposed (Eng, U.S. Patent No. 5,424,286).

C-terminally truncated exendin peptides such as exendin[9-39], a carboxyamidated molecule, and fragments 3-39 through 9-39 have been reported to be potent and selective antagonists of GLP-1 (Goke, et al., J. Biol. Chem., 268:19650-55, 1993; Raufman, J.P., et al., J. Biol. Chem. 266:2897-902, 1991; Schepp, W., et al., Eur. J. Pharm. 269:183-91, 1994; Montrose-Rafizadeh, et al., Diabetes, 45(Suppl. 2):152A, 1996). Exendin[9-39] is said to block endogenous GLP-1 in vivo, resulting in reduced insulin secretion. Wang, et al., J. Clin. Invest., 95:417-21, 1995; D'Alessio, et al., J. Clin. Invest., 97:133-38, 1996). The receptor apparently responsible for the insulinotropic effect of GLP-1 has reportedly been cloned from rat pancreatic islet cell (Thorens, B., Proc. Natl. Acad. Sci. USA 89:8641-8645, 1992). Exendins and exendin[9-39] are said to bind to the cloned GLP-1 receptor (rat pancreatic  $\beta$ -cell GLP-1 receptor (Fehmann HC, et al., Peptides 15 (3): 453-6, 1994) and human GLP-1 receptor (Thorens B, et al., Diabetes 42 (11): 1678-82, 1993). In cells transfected with the cloned GLP-1 receptor, exendin-4 is reportedly an agonist, i.e., it increases cAMP, while exendin[9-39] is identified as an antagonist, i.e., it blocks the stimulatory actions of exendin-4 and GLP-1. Id.

Exendin[9-39] is also reported to act as an antagonist of the full length exendins, inhibiting stimulation of pancreatic acinar cells by exendin-3 and exendin-4 (Raufman, et al., J. Biol. Chem. 266:2897-902,



1991; Raufman, et al., J. Biol. Chem., 266:21432-37, 1992). It is also reported that exendin[9-39] inhibits the stimulation of plasma insulin levels by exendin-4, and inhibits the somatostatin release-stimulating and gastrin release-inhibiting activities of exendin-4 and GLP-1 (Kolligs, F., et al., Diabetes, 44:16-19, 1995; Eissele, et al., Life Sciences, 55:629-34, 1994).

Exendins have recently been found to inhibit gastric emptying (U.S.S.N. 08/694,954, filed August 8, 1996, which enjoys common ownership with the present invention and is hereby incorporated by reference).

Exendin [9-39] has been used to investigate the physiological relevance of central GLP-1 in control of food intake (Turton, M.D. et al. Nature 379:69-72, 1996).

GLP-1 administered by intracerebroventricular injection inhibits food intake in rats. This satiety-inducing effect of GLP-1 delivered ICV is reported to be inhibited by ICV injection of exendin [9-39] (Turton, supra). However, it has been reported that GLP-1 does not inhibit food intake in mice when administered by peripheral injection (Turton, M.D., Nature 379:69-72, 1996; Bhavsar, S.P., Soc. Neurosci. Abstr. 21:460 (188.8), 1995).

#### Obesity and Hypernutrition

Obesity, excess adipose tissue, is becoming increasingly prevalent in developed societies. For example, approximately 30% of adults in the U.S. were estimated to be 20 percent above desirable body weight -- an accepted measure of obesity sufficient to impact a health risk (*Harrison's Principles of Internal Medicine*

12th Edition, McGraw Hill, Inc. (1991) p. 411). The pathogenesis of obesity is believed to be multifactorial but the basic problem is that in obese subjects food intake and energy expenditure do not come into balance until there is excess adipose tissue. Attempts to reduce food intake, or hypernutrition, are usually fruitless in the medium term because the weight loss induced by dieting results in both increased appetite and decreased energy expenditure (Leibel et al., (1995) *New England Journal of Medicine* 322: 621-628). The intensity of physical exercise required to expend enough energy to materially lose adipose mass is too great for most people to undertake on a sufficiently frequent basis. Thus, obesity is currently a poorly treatable, chronic, essentially intractable metabolic disorder. Not only is obesity itself believed by some to be undesirable for cosmetic reasons, but obesity also carries serious risk of comorbidities including, Type 2 diabetes, increased cardiac risk, hypertension, atherosclerosis, degenerative arthritis, and increased incidence of complications of surgery involving general anesthesia. Obesity due to hypernutrition is also a risk factor for the group of conditions called insulin resistance syndrome, or "syndrome X." In syndrome X, it has been reported that there is a linkage between insulin resistance and hypertension. (Watson N. and Sandler M., *Curr. Med. Res. Opin.*, 12(6):374-378 (1991); Kodama J. et al., *Diabetes Care*, 13(11):1109-1111 (1990); Lithell et al., *J. Cardiovasc. Pharmacol.*, 15 Suppl. 5:S46-S52 (1990)).

In those few subjects who do succeed in losing weight, by about 10 percent of body weight, there can be striking improvements in co-morbid conditions, most especially Type 2 diabetes in which dieting and weight loss are the primary therapeutic modality, albeit relatively ineffective in many patients for the reasons stated above. Reducing food intake in obese subjects would decrease the plasma glucose level, the plasma lipid level, and the cardiac risk in these subjects.

Hypernutrition is also the result of, and the psychological cause of, many eating disorders. Reducing food intake would also be beneficial in the treatment of such disorders.

Thus, it can be appreciated that an effective means to reduce food intake is a major challenge and a superior method of treatment would be of great utility. Such a method, and compounds and compositions which are useful therefor, have been invented and are described and claimed herein.

#### SUMMARY OF THE INVENTION

The present invention concerns the surprising discovery that exendins and exendin agonists have a profound and prolonged effect on inhibiting food intake.

The present invention is directed to novel methods for treating conditions or disorders associated with hypernutrition, comprising the administration of an exendin, for example, exendin-3 [SEQ ID NO. 1: His Ser Asp

Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu  
Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro  
Ser Ser Gly Ala Pro Pro Pro Ser], or exendin-4 [SEQ ID NO.  
2: His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
5 Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn  
Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser], or other  
compounds which effectively bind to the receptor at which  
exendin exerts its action on reducing food intake. These  
methods will be useful in the treatment of, for example,  
10 obesity, diabetes, including Type II or non-insulin  
dependent diabetes, eating disorders, and insulin-  
resistance syndrome.

In a first aspect, the invention features a method of  
treating conditions or disorders which can be alleviated  
15 by reducing food intake in a subject comprising  
administering to the subject a therapeutically effective  
amount of an exendin or an exendin agonist. By an "exendin  
agonist" is meant a compound that mimics the effects of  
exendin on the reduction of food intake by binding to the  
20 receptor or receptors where exendin causes this effect.  
Preferred exendin agonist compounds include those described  
in United States Provisional Patent Application Serial No.  
60/055,404, entitled, "Novel Exendin Agonist Compounds,"  
filed August 8, 1997; United States Provisional Patent  
25 Application Serial No. 60/065,442, entitled, "Novel Exendin  
Agonist Compounds," filed November 14, 1997; and United  
States Provisional Patent Application Serial No.  
60/066,029, entitled, "Novel Exendin Agonist Compounds,"  
filed November 14, 1997; all of which enjoy common

ownership with the present application and all of which are incorporated by this reference into the present application as though fully set forth herein. By "condition or disorder which can be alleviated by reducing food intake" is meant any condition or disorder in a subject that is either caused by, complicated by, or aggravated by a relatively high food intake, or that can be alleviated by reducing food intake. Such conditions or disorders include, but are not limited to, obesity, diabetes, including Type II diabetes, eating disorders, and insulin-resistance syndrome.

Thus, in a first embodiment, the present invention provides a method for treating conditions or disorders which can be alleviated by reducing food intake in a subject comprising administering to said subject a therapeutically effective amount of an exendin or an exendin agonist. Preferred exendin agonist compounds include those described in U.S. Provisional Patent Application Serial Nos. 60/055,404; 60/065,442; and 60/066,029, which have been incorporated by reference in the present application. Preferably, the subject is a vertebrate, more preferably a mammal, and most preferably a human. In preferred aspects, the exendin or exendin agonist is administered parenterally, more preferably by injection. In a most preferred aspect, the injection is a peripheral injection. Preferably, about 10  $\mu$ g-30  $\mu$ g to about 5 mg of the exendin or exendin agonist is administered per day. More preferably, about 10-30  $\mu$ g to about 2mg, or about 10-30  $\mu$ g to about 1mg of the exendin or

exendin agonist is administered per day. Most preferably, about 30  $\mu\text{g}$  to about 500  $\mu\text{g}$  of the exendin or exendin agonist is administered per day.

5 In various preferred embodiments of the invention, the condition or disorder is obesity, diabetes, preferably Type II diabetes, an eating disorder, or insulin-resistance syndrome.

10 In other preferred aspects of the invention, a method is provided for reducing the appetite of a subject comprising administering to said subject an appetite-lowering amount of an exendin or an exendin agonist.

15 In yet other preferred aspects, a method is provided for lowering plasma lipids comprising administering to said subject a therapeutically effective amount of an exendin or an exendin agonist.

20 The methods of the present invention may also be used to reduce the cardiac risk of a subject comprising administering to said subject a therapeutically effective amount of an exendin or an exendin agonist. In one preferred aspect, the exendin or exendin agonist used in the methods of the present invention is exendin-3. In another preferred aspect, said exendin is exendin-4. Other preferred exendin agonists include exendin-4 (1-30) [SEQ ID NO 6: His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln  
25 Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly], exendin-4 (1-30) amide [SEQ ID NO 7: His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly-NH<sub>2</sub>], exendin-4 (1-28) amide [SEQ ID NO 40: His Gly Glu Gly Thr

Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg  
 Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>], <sup>14</sup>Leu, <sup>25</sup>Phe exendin-4  
 amide [SEQ ID NO 9: His Gly Glu Gly Thr Phe Thr Ser Asp Leu  
 Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe  
 5 Leu Lys Asn Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser-  
 NH<sub>2</sub>], <sup>14</sup>Leu, <sup>25</sup>Phe exendin-4 (1-28) amide [SEQ ID NO 41: His  
 Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu  
 Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>], and  
<sup>14</sup>Leu, <sup>22</sup>Ala, <sup>25</sup>Phe exendin-4 (1-28) amide [SEQ ID NO 8: His Gly  
 10 Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu  
 Ala Val Arg Leu Ala Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>].

In the methods of the present invention, the extendins  
 and exendin agonists may be administered separately or  
 together with one or more other compounds and compositions  
 15 that exhibit a long term or short-term satiety action,  
 including, but not limited to other compounds and  
 compositions that comprise an amylin agonist,  
 cholecystokinin (CCK), or a leptin (ob protein). Suitable  
 amylin agonists include, for example, [<sup>25,28,29</sup>Pro-]-human  
 20 amylin (also known as "pramlintide," and previously  
 referred to as "AC-137") as described in "Amylin Agonist  
 Peptides and Uses Therefor," U.S. Patent No. 5,686,511,  
 issued November 11, 1997, and salmon calcitonin. The CCK  
 used is preferably CCK octopeptide (CCK-8). Leptin is  
 25 discussed in, for example, Pelleymounter, M.A., et al.  
Science 269:540-43 (1995); Halaas, J.L., et al. Science  
 269:543-46 (1995); and Campfield, L.A., et al. Eur. J.  
Pharmac. 262:133-41 (1994).

In other embodiments of the invention is provided a pharmaceutical composition for use in the treatment of conditions or disorders which can be alleviated by reducing food intake comprising a therapeutically effective amount of an exendin or exendin agonist in association with a pharmaceutically acceptable carrier. Preferably, the pharmaceutical composition comprises a therapeutically effective amount for a human subject.

The pharmaceutical composition may preferably be used for reducing the appetite of a subject, reducing the weight of a subject, lowering the plasma lipid level of a subject, or reducing the cardiac risk of a subject. Those of skill in the art will recognize that the pharmaceutical composition will preferably comprise a therapeutically effective amount of an exendin or exendin agonist to accomplish the desired effect in the subject.

The pharmaceutical compositions may further comprise one or more other compounds and compositions that exhibit a long-term or short-term satiety action, including, but not limited to other compounds and compositions that comprise an amylin agonist, CCK, preferably CCK-8, or leptin. Suitable amylin agonists include, for example, [<sup>25,28,29</sup>Pro]-human amylin and salmon calcitonin.

In one preferred aspect, the pharmaceutical composition comprises exendin-3. In another preferred aspect, the pharmaceutical composition comprises exendin-4.

In other preferred aspects, the pharmaceutical compositions comprises a peptide selected from: exendin-4 (1-30), exendin-4 (1-30) amide, exendin-4 (1-28) amide,



<sup>14</sup>Leu,<sup>25</sup>Phe exendin-4 amide, <sup>14</sup>Leu,<sup>25</sup>Phe exendin-4 (1-28) amide, and <sup>14</sup>Leu,<sup>22</sup>Ala,<sup>25</sup>Phe exendin-4 (1-28) amide.

5

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graphical depiction of the change of food intake in normal mice after intraperitoneal injection of exendin-4 and GLP-1.

10

Figure 2 is a graphical depiction of the change of food intake in obese mice after intraperitoneal injection of exendin-4.

Figure 3 is a graphical depiction of the change of food intake in rats after intracerebroventricular injection of exendin-4

15

Figure 4 is a graphical depiction of the change of food intake in normal mice after intraperitoneal injection of exendin-4 (1-30) ("Compound 1").

20

Figure 5 is a graphical depiction of the change of food intake in normal mice after intraperitoneal injection of exendin-4 (1-30) amide ("Compound 2").

Figure 6 is a graphical depiction of the change of food intake in normal mice after intraperitoneal injection of exendin-4 (1-28) amide ("Compound 3").

25

Figure 7 is a graphical depiction of the change of food intake in normal mice after intraperitoneal injection of <sup>14</sup>Leu,<sup>25</sup>Phe exendin-4 amide ("Compound 4").

Figure 8 is a graphical depiction of the change of food intake in normal mice after intraperitoneal injection of <sup>14</sup>Leu,<sup>25</sup>Phe exendin-4 (1-28) amide ("Compound 5").

Figure 10 depicts the amino acid sequences for certain  
exendin agonist compounds useful in the present invention  
[SEQ ID NOS 9-39].

Exendins and exendin agonists are useful as described

## Exendin Agonist Compounds

1 5 10  
Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Gly Thr Xaa<sub>4</sub> Xaa<sub>5</sub> Xaa<sub>6</sub> Xaa<sub>7</sub> Xaa<sub>8</sub>  
15 20  
Ser Lys Gln Xaa<sub>9</sub> Glu Glu Glu Ala Val Arg Leu  
25 30  
Xaa<sub>10</sub> Xaa<sub>11</sub> Xaa<sub>12</sub> Xaa<sub>13</sub> Leu Lys Asn Gly Gly Xaa<sub>14</sub>  
35  
Ser Ser Gly Ala Xaa<sub>15</sub> Xaa<sub>16</sub> Xaa<sub>17</sub> Xaa<sub>18</sub>-Z

wherein Xaa<sub>1</sub> is His, Arg or Tyr; Xaa<sub>2</sub> is Ser, Gly, Ala or Thr; Xaa<sub>3</sub> is Asp or Glu; Xaa<sub>4</sub> is Phe, Tyr or naphthylalanine; Xaa<sub>5</sub> is Thr or Ser; Xaa<sub>6</sub> is Ser or Thr; Xaa<sub>7</sub> is Asp or Glu; Xaa<sub>8</sub> is Leu, Ile, Val, pentylglycine or Met; Xaa<sub>9</sub> is Leu, Ile, pentylglycine, Val or Met; Xaa<sub>10</sub> is Phe, Tyr or naphthylalanine; Xaa<sub>11</sub> is Ile, Val, Leu, pentylglycine, tert-butylglycine or Met; Xaa<sub>12</sub> is Glu or Asp; Xaa<sub>13</sub> is Trp, Phe, Tyr, or naphthylalanine; Xaa<sub>14</sub>, Xaa<sub>15</sub>, Xaa<sub>16</sub> and Xaa<sub>17</sub> are independently Pro, homoproline, 3Hyp, 4Hyp, thioproline, N-alkylglycine, N-alkylpentylglycine or N-alkylalanine; Xaa<sub>18</sub> is Ser, Thr or Tyr; and Z is -OH or -NH<sub>2</sub>; with the proviso that the compound is not exendin-3 or exindin-4.

Preferred N-alkyl groups for N-alkylglycine, N-alkylpentylglycine and N-alkylalanine include lower alkyl groups preferably of 1 to about 6 carbon atoms, more preferably of 1 to 4 carbon atoms. Suitable compounds include those listed in Figure 10 having amino acid sequences of SEQ. ID. NOS. 9 to 39.

Preferred exendin agonist compounds include those wherein Xaa<sub>1</sub> is His or Tyr. More preferably Xaa<sub>1</sub> is His.

Preferred are those compounds wherein Xaa<sub>2</sub> is Gly.

Preferred are those compounds wherein Xaa<sub>8</sub> is Leu, pentylglycine or Met.

Preferred compounds include those wherein Xaa<sub>13</sub> is Trp or Phe.

Also preferred are compounds where Xaa<sub>4</sub> is Phe or naphthylalanine; Xaa<sub>11</sub> is Ile or Val and Xaa<sub>14</sub>, Xaa<sub>15</sub>, Xaa<sub>16</sub>

and Xaa<sub>17</sub>, are independently selected from Pro, homoproline, thioproline or N-alkylalanine. Preferably N-alkylalanine has a N-alkyl group of 1 to about 6 carbon atoms.

According to an especially preferred aspect, Xaa<sub>15</sub>,  
5 Xaa<sub>16</sub> and Xaa<sub>17</sub>, are the same amino acid residue.

Preferred are compounds wherein Xaa<sub>18</sub> is Ser or Tyr, more preferably Ser.

Preferably Z is -NH<sub>2</sub>.

According to one aspect, preferred are compounds of  
10 formula (I) wherein Xaa<sub>1</sub> is His or Tyr, more preferably His; Xaa<sub>2</sub> is Gly; Xaa<sub>4</sub> is Phe or naphthylalanine; Xaa<sub>5</sub> is Leu, pentylglycine or Met; Xaa<sub>10</sub> is Phe or naphthylalanine; Xaa<sub>11</sub> is Ile or Val; Xaa<sub>14</sub>, Xaa<sub>15</sub>, Xaa<sub>16</sub> and Xaa<sub>17</sub>, are  
independently selected from Pro, homoproline, thioproline  
15 or N-alkylalanine; and Xaa<sub>18</sub> is Ser or Tyr, more preferably Ser. More preferably Z is -NH<sub>2</sub>.

According to an especially preferred aspect,  
especially preferred compounds include those of formula  
(I) wherein: Xaa<sub>1</sub> is His or Arg; Xaa<sub>2</sub> is Gly; Xaa<sub>3</sub> is Asp  
20 or Glu; Xaa<sub>4</sub> is Phe or naphthylalanine; Xaa<sub>5</sub> is Thr or Ser;  
Xaa<sub>6</sub> is Ser or Thr; Xaa<sub>7</sub> is Asp or Glu; Xaa<sub>8</sub> is Leu or pentylglycine; Xaa<sub>9</sub> is Leu or pentylglycine; Xaa<sub>10</sub> is Phe or naphthylalanine; Xaa<sub>11</sub> is Ile, Val or t-butyltylglycine; Xaa<sub>12</sub> is Glu or Asp; Xaa<sub>13</sub> is Trp or Phe; Xaa<sub>14</sub>, Xaa<sub>15</sub>, Xaa<sub>16</sub>,  
25 and Xaa<sub>17</sub>, are independently Pro, homoproline, thioproline, or N-methylalanine; Xaa<sub>18</sub> is Ser or Tyr; and Z is -OH or -NH<sub>2</sub>; with the proviso that the compound does not have the formula of either SEQ. ID. NOS. 1 or 2. More preferably Z

is -NH<sub>2</sub>. Especially preferred compounds include those having the amino acid sequence of SEQ. ID. NOS. 9, 10, 21, 22, 23, 26, 28, 34, 35 and 39.

5           According to an especially preferred aspect, provided are compounds where Xaa<sub>1</sub> is Leu, Ile, Val or pentylglycine, more preferably Leu or pentylglycine, and Xaa<sub>13</sub> is Phe, Tyr or naphthylalanine, more preferably Phe or naphthylalanine. These compounds will exhibit advantageous  
10           duration of action and be less subject to oxidative degradation, both in vitro and in vivo, as well as during synthesis of the compound.

            Exendin agonist compounds also include those described in U.S. Provisional Application No. 60/065,442,  
15           including compounds of the formula (II) [SEQ ID NO. 4]:

Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Gly Xaa<sub>5</sub> Xaa<sub>6</sub> Xaa<sub>7</sub> Xaa<sub>8</sub> Xaa<sub>9</sub> Xaa<sub>10</sub>  
Xaa<sub>11</sub> Xaa<sub>12</sub> Xaa<sub>13</sub> Xaa<sub>14</sub> Xaa<sub>15</sub> Xaa<sub>16</sub> Xaa<sub>17</sub> Ala Xaa<sub>19</sub> Xaa<sub>20</sub>  
Xaa<sub>21</sub> Xaa<sub>22</sub> Xaa<sub>23</sub> Xaa<sub>24</sub> Xaa<sub>25</sub> Xaa<sub>26</sub> Xaa<sub>27</sub> Xaa<sub>28</sub>-Z<sub>1</sub>; wherein

20

Xaa<sub>1</sub> is His, Arg or Tyr;

Xaa<sub>2</sub> is Ser, Gly, Ala or Thr;

Xaa<sub>3</sub> is Asp or Glu;

Xaa<sub>5</sub> is Ala or Thr;

25           Xaa<sub>6</sub> is Ala, Phe, Tyr or naphthylalanine;

Xaa<sub>7</sub> is Thr or Ser;

Xaa<sub>8</sub> is Ala, Ser or Thr;

Xaa<sub>9</sub> is Asp or Glu;

- Xaa<sub>30</sub> is Ala, Leu, Ile, Val, pentylglycine or Met;  
 Xaa<sub>31</sub> is Ala or Ser;  
 Xaa<sub>32</sub> is Ala or Lys;  
 Xaa<sub>33</sub> is Ala or Gln;
- 5 Xaa<sub>34</sub> is Ala, Leu, Ile, pentylglycine, Val or Met;  
 Xaa<sub>35</sub> is Ala or Glu;  
 Xaa<sub>36</sub> is Ala or Glu;  
 Xaa<sub>37</sub> is Ala or Glu;  
 Xaa<sub>38</sub> is Ala or Val;
- 10 Xaa<sub>39</sub> is Ala or Arg;  
 Xaa<sub>40</sub> is Ala or Leu;  
 Xaa<sub>41</sub> is Ala, Phe, Tyr or naphthylalanine;  
 Xaa<sub>42</sub> is Ile, Val, Leu, pentylglycine, tert-butylglycine  
 or Met;
- 15 Xaa<sub>43</sub> is Ala, Glu or Asp;  
 Xaa<sub>44</sub> is Ala, Trp, Phe, Tyr or naphthylalanine;  
 Xaa<sub>45</sub> is Ala or Leu;  
 Xaa<sub>46</sub> is Ala or Lys;  
 Xaa<sub>47</sub> is Ala or Asn;
- 20 Z<sub>1</sub> is -OH,  
       -NH<sub>2</sub>  
       Gly-Z<sub>2</sub>,  
       Gly Gly-Z<sub>2</sub>,  
       Gly Gly Xaa<sub>31</sub>-Z<sub>2</sub>,
- 25 Gly Gly Xaa<sub>31</sub> Ser-Z<sub>2</sub>,  
       Gly Gly Xaa<sub>31</sub> Ser Ser-Z<sub>2</sub>,  
       Gly Gly Xaa<sub>31</sub> Ser Ser Gly-Z<sub>2</sub>,  
       Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub>-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub> Xaa<sub>37</sub>-Z<sub>2</sub> or

Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub> Xaa<sub>37</sub> Xaa<sub>38</sub>-Z<sub>2</sub>;

Xaa<sub>31</sub>, Xaa<sub>36</sub>, Xaa<sub>37</sub> and Xaa<sub>38</sub> are independently Pro,

5 homoproline, 3Hyp, 4Hyp, thioproline,

N-alkylglycine, N-alkylpentylglycine or

N-alkylalanine; and

Z<sub>2</sub> is -OH or -NH<sub>2</sub>;

provided that no more than three of Xaa<sub>3</sub>, Xaa<sub>5</sub>, Xaa<sub>6</sub>, Xaa<sub>8</sub>,

10 Xaa<sub>10</sub>, Xaa<sub>11</sub>, Xaa<sub>12</sub>, Xaa<sub>13</sub>, Xaa<sub>14</sub>, Xaa<sub>15</sub>, Xaa<sub>16</sub>, Xaa<sub>17</sub>, Xaa<sub>19</sub>,

Xaa<sub>20</sub>, Xaa<sub>21</sub>, Xaa<sub>24</sub>, Xaa<sub>25</sub>, Xaa<sub>26</sub>, Xaa<sub>27</sub> and Xaa<sub>29</sub> are Ala.

Preferred N-alkyl groups for N-alkylglycine, N-

alkylpentylglycine and N-alkylalanine include lower alkyl

groups preferably of 1 to about 6 carbon atoms, more

15 preferably of 1 to 4 carbon atoms.

Preferred exendin agonist compounds include those

wherein Xaa<sub>1</sub> is His or Tyr. More preferably Xaa<sub>1</sub> is His.

Preferred are those compounds wherein Xaa<sub>2</sub> is Gly.

Preferred are those compounds wherein Xaa<sub>14</sub> is Leu,

20 pentylglycine or Met.

Preferred compounds are those wherein Xaa<sub>25</sub> is Trp or Phe.

Preferred compounds are those where Xaa<sub>6</sub> is Phe or naphthylalanine; Xaa<sub>22</sub> is Phe or naphthylalanine and

25 Xaa<sub>23</sub> is Ile or Val.

Preferred are compounds wherein Xaa<sub>31</sub>, Xaa<sub>36</sub>, Xaa<sub>37</sub> and Xaa<sub>38</sub> are independently selected from Pro, homoproline, thioproline and N-alkylalanine.

Preferably  $Z_1$  is  $-NH_2$ .

Preferable  $Z_2$  is  $-NH_2$ .

According to one aspect, preferred are compounds of formula (I) wherein  $Xaa_1$  is His or Tyr, more preferably His;  $Xaa_2$  is Gly;  $Xaa_6$  is Phe or naphthylalanine;  $Xaa_{14}$  is Leu, pentylglycine or Met;  $Xaa_{22}$  is Phe or naphthylalanine;  $Xaa_{23}$  is Ile or Val;  $Xaa_{31}$ ,  $Xaa_{36}$ ,  $Xaa_{37}$  and  $Xaa_{38}$  are independently selected from Pro, homoproline, thioproline or N-alkylalanine. More preferably  $Z_1$  is  $-NH_2$ .

According to an especially preferred aspect, especially preferred compounds include those of formula (I) wherein:  $Xaa_1$  is His or Arg;  $Xaa_2$  is Gly or Ala;  $Xaa_3$  is Asp or Glu;  $Xaa_5$  is Ala or Thr;  $Xaa_6$  is Ala, Phe or naphthylalanine;  $Xaa_7$  is Thr or Ser;  $Xaa_8$  is Ala, Ser or Thr;  $Xaa_9$  is Asp or Glu;  $Xaa_{10}$  is Ala, Leu or pentylglycine;  $Xaa_{11}$  is Ala or Ser;  $Xaa_{12}$  is Ala or Lys;  $Xaa_{13}$  is Ala or Gln;  $Xaa_{14}$  is Ala, Leu or pentylglycine;  $Xaa_{15}$  is Ala or Glu;  $Xaa_{16}$  is Ala or Glu;  $Xaa_{17}$  is Ala or Glu;  $Xaa_{19}$  is Ala or Val;  $Xaa_{20}$  is Ala or Arg;  $Xaa_{21}$  is Ala or Leu;  $Xaa_{22}$  is Phe or naphthylalanine;  $Xaa_{23}$  is Ile, Val or tert-butylglycine;  $Xaa_{24}$  is Ala, Glu or Asp;  $Xaa_{25}$  is Ala, Trp or Phe;  $Xaa_{26}$  is Ala or Leu;  $Xaa_{27}$  is Ala or Lys;  $Xaa_{28}$  is Ala or Asn;  $Z_1$  is  $-OH$ ,  $-NH_2$ , Gly- $Z_2$ , Gly Gly- $Z_2$ , Gly Gly  $Xaa_{31}$ - $Z_2$ , Gly Gly  $Xaa_{31}$  Ser- $Z_2$ , Gly Gly  $Xaa_{31}$  Ser Ser- $Z_2$ , Gly Gly  $Xaa_{31}$  Ser Ser Gly- $Z_2$ , Gly Gly  $Xaa_{31}$  Ser Ser Gly Ala- $Z_2$ , Gly Gly  $Xaa_{31}$  Ser Ser Gly Ala  $Xaa_{36}$ - $Z_2$ , Gly Gly  $Xaa_{31}$  Ser Ser Gly Ala  $Xaa_{36}$   $Xaa_{37}$ - $Z_2$ , Gly Gly  $Xaa_{31}$  Ser Ser Gly Ala  $Xaa_{36}$   $Xaa_{37}$   $Xaa_{38}$ - $Z_2$ ;  $Xaa_{31}$ ,  $Xaa_{36}$ ,  $Xaa_{37}$  and  $Xaa_{38}$  being independently Pro homoproline, thioproline or N-



methyllalanine; and Z<sub>2</sub> being -OH or -NH<sub>2</sub>; provided that no more than three of Xaa<sub>3</sub>, Xaa<sub>5</sub>, Xaa<sub>6</sub>, Xaa<sub>8</sub>, Xaa<sub>10</sub>, Xaa<sub>11</sub>, Xaa<sub>12</sub>, Xaa<sub>13</sub>, Xaa<sub>14</sub>, Xaa<sub>15</sub>, Xaa<sub>16</sub>, Xaa<sub>17</sub>, Xaa<sub>19</sub>, Xaa<sub>20</sub>, Xaa<sub>21</sub>, Xaa<sub>24</sub>, Xaa<sub>25</sub>, Xaa<sub>26</sub>, Xaa<sub>27</sub> and Xaa<sub>28</sub> are Ala. Especially  
 5 preferred compounds include those having the amino acid sequence of SEQ. ID. NOS. 40-61.

According to an especially preferred aspect, provided are compounds where Xaa<sub>14</sub> is Leu, Ile, Val or pentylglycine, more preferably Leu or pentylglycine, and  
 10 Xaa<sub>25</sub> is Phe, Tyr or naphthylalanine, more preferably Phe or naphthylalanine. These compounds will be less susceptible to oxidative degradation, both in vitro and in vivo, as well as during synthesis of the compound.

Exendin agonist compounds also include those  
 15 described in U.S. Provisional Application No. 60/066,029, including compounds of the formula (III) [SEQ ID NO. 5]:

Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Xaa<sub>4</sub> Xaa<sub>5</sub> Xaa<sub>6</sub> Xaa<sub>7</sub> Xaa<sub>8</sub> Xaa<sub>9</sub> Xaa<sub>10</sub>  
 Xaa<sub>11</sub> Xaa<sub>12</sub> Xaa<sub>13</sub> Xaa<sub>14</sub> Xaa<sub>15</sub> Xaa<sub>16</sub> Xaa<sub>17</sub> Ala Xaa<sub>19</sub> Xaa<sub>20</sub>  
 20 Xaa<sub>21</sub> Xaa<sub>22</sub> Xaa<sub>23</sub> Xaa<sub>24</sub> Xaa<sub>25</sub> Xaa<sub>26</sub> Xaa<sub>27</sub> Xaa<sub>28</sub>-Z<sub>1</sub>; wherein

Xaa<sub>1</sub> is His, Arg, Tyr, Ala, Norval, Val  
 or Norleu;

Xaa<sub>2</sub> is Ser, Gly, Ala or Thr;

25 Xaa<sub>3</sub> is Ala, Asp or Glu;

Xaa<sub>4</sub> is Ala, Norval, Val, Norleu or Gly;

Xaa<sub>5</sub> is Ala or Thr;

Xaa<sub>6</sub> is Phe, Tyr or naphthylalanine;

- Xaa<sub>1</sub> is Thr or Ser;  
 Xaa<sub>2</sub> is Ala, Ser or Thr;  
 Xaa<sub>3</sub> is Ala, Norval, Val, Norleu, Asp or Glu;  
 Xaa<sub>10</sub> is Ala, Leu, Ile, Val, pentylglycine or Met;  
 5 Xaa<sub>11</sub> is Ala or Ser;  
 Xaa<sub>12</sub> is Ala or Lys;  
 Xaa<sub>13</sub> is Ala or Gln;  
 Xaa<sub>14</sub> is Ala, Leu, Ile, pentylglycine, Val or Met;  
 Xaa<sub>15</sub> is Ala or Glu;  
 10 Xaa<sub>16</sub> is Ala or Glu;  
 Xaa<sub>17</sub> is Ala or Glu;  
 Xaa<sub>19</sub> is Ala or Val;  
 Xaa<sub>20</sub> is Ala or Arg;  
 Xaa<sub>21</sub> is Ala or Leu;  
 15 Xaa<sub>22</sub> is Phe, Tyr or naphthylalanine;  
 Xaa<sub>23</sub> is Ile, Val, Leu, pentylglycine, tert-butylglycine or Met;  
 Xaa<sub>24</sub> is Ala, Glu or Asp;  
 Xaa<sub>25</sub> is Ala, Trp, Phe, Tyr or naphthylalanine;  
 20 Xaa<sub>26</sub> is Ala or Leu;  
 Xaa<sub>27</sub> is Ala or Lys;  
 Xaa<sub>28</sub> is Ala or Asn;  
 Z<sub>1</sub> is -OH,  
       -NH<sub>2</sub>,  
 25 Gly-Z<sub>2</sub>,  
       Gly Gly-Z<sub>2</sub>,  
       Gly Gly Xaa<sub>31</sub>-Z<sub>2</sub>,  
       Gly Gly Xaa<sub>31</sub> Ser-Z<sub>2</sub>,

Gly Gly Xaa<sub>31</sub> Ser Ser-Z<sub>2</sub>,  
 Gly Gly Xaa<sub>31</sub> Ser Ser Gly-Z<sub>2</sub>,  
 Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala-Z<sub>2</sub>,  
 Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub>-Z<sub>2</sub>,  
 5 Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub> Xaa<sub>37</sub>-Z<sub>2</sub>,  
 Gly Gly Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub> Xaa<sub>37</sub> Xaa<sub>38</sub>-Z<sub>2</sub> or Gly  
 Gly Xaa<sub>31</sub> Ser Ser Gly Ala Xaa<sub>36</sub> Xaa<sub>37</sub> Xaa<sub>38</sub> Xaa<sub>39</sub>-Z<sub>2</sub>; wherein  
 Xaa<sub>31</sub>, Xaa<sub>36</sub>, Xaa<sub>37</sub> and Xaa<sub>38</sub> are independently  
 Pro, homoproline, 3Hyp, 4Hyp, thioproline,  
 10 N-alkylglycine, N-alkylpentylglycine or  
 N-alkylalanine; and  
 Z<sub>2</sub> is -OH or -NH<sub>2</sub>;

provided that no more than three of Xaa<sub>3</sub>, Xaa<sub>4</sub>, Xaa<sub>5</sub>, Xaa<sub>6</sub>,  
 Xaa<sub>8</sub>, Xaa<sub>9</sub>, Xaa<sub>10</sub>, Xaa<sub>11</sub>, Xaa<sub>12</sub>, Xaa<sub>13</sub>, Xaa<sub>14</sub>, Xaa<sub>15</sub>, Xaa<sub>16</sub>,  
 15 Xaa<sub>17</sub>, Xaa<sub>19</sub>, Xaa<sub>20</sub>, Xaa<sub>21</sub>, Xaa<sub>24</sub>, Xaa<sub>25</sub>, Xaa<sub>26</sub>, Xaa<sub>27</sub> and Xaa<sub>28</sub>  
 are Ala; and provided also that, if Xaa<sub>1</sub> is His, Arg or  
 Tyr, then at least one of Xaa<sub>3</sub>, Xaa<sub>4</sub> and Xaa<sub>9</sub> is Ala.

### Definitions

20 In accordance with the present invention and as used  
 herein, the following terms are defined to have the  
 following meanings, unless explicitly stated otherwise.

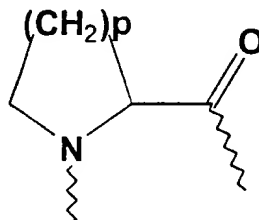
The term "amino acid" refers to natural amino acids,  
 unnatural amino acids, and amino acid analogs, all in  
 25 their D and L stereoisomers if their structure allow such  
 stereoisomeric forms. Natural amino acids include alanine  
 (Ala), arginine (Arg), asparagine (Asn), aspartic acid  
 (Asp), cysteine (Cys), glutamine (Gln), glutamic acid  
 (Glu), glycine (Gly), histidine (His), isoleucine (Ile),

leucine (Leu), Lysine (Lys), methionine (Met),  
phenylalanine (Phe), proline (Pro), serine (Ser),  
threonine (Thr), typtophan (Trp), tyrosine (Tyr) and  
valine (Val). Unnatural amino acids include, but are not  
5 limited to azetidinecarboxylic acid, 2-aminoadipic acid,  
3-aminoadipic acid, beta-alanine, aminopropionic acid, 2-  
aminobutyric acid, 4-aminobutyric acid, 6-aminocaproic  
acid, 2-aminoheptanoic acid, 2-aminoisobutyric acid, 3-  
aminoisobutyric acid, 2-aminopimelic acid, tertiary-  
10 butylglycine, 2,4-diaminoisobutyric acid, desmosine, 2,2'-  
diaminopimelic acid, 2,3-diaminopropionic acid, N-  
ethylglycine, N-ethylasparagine, homoproline,  
hydroxylysine, allo-hydroxylysine, 3-hydroxyproline, 4-  
hydroxyproline, isodesmosine, allo-isoleucine, N-  
15 methylalanine, N-methylglycine, N-methylisoleucine, N-  
methylpentylglycine, N-methylvaline, naphthalanine,  
norvaline, norleucine, ornithine, pentylglycine, pipecolic  
acid and thioproline. Amino acid analogs include the  
natural and unnatural amino acids which are chemically  
20 blocked, reversibly or irreversibly, or modified on their  
N-terminal amino group or their side-chain groups, as for  
example, methionine sulfoxide, methionine sulfone, S-  
(carboxymethyl)-cysteine, S-(carboxymethyl)-cysteine  
sulfoxide and S-(carboxymethyl)-cysteine sulfone.

25       The term "amino acid analog" refers to an amino acid  
wherein either the C-terminal carboxy group, the N-  
terminal amino group or side-chain functional group has  
been chemically codified to another functional group. For  
example, aspartic acid-(beta-methyl ester) is an amino

acid analog of aspartic acid; N-ethylglycine is an amino acid analog of glycine; or alanine carboxamide is an amino acid analog of alanine.

The term "amino acid residue" refers to radicals having the structure: (1)  $-C(O)-R-NH-$ , wherein R typically is  $-CH(R')$ -, wherein R' is an amino acid side chain, typically H or a carbon containing substituent; or (2),



10

wherein p is 1, 2 or 3 representing the azetidinecarboxylic acid, proline or pipecolic acid residues, respectively.

The term "lower" referred to herein in connection with organic radicals such as alkyl groups defines such groups with up to and including about 6, preferably up to and including 4 and advantageously one or two carbon atoms. Such groups may be straight chain or branched chain.

"Pharmaceutically acceptable salt" includes salts of the compounds described herein derived from the combination of such compounds and an organic or inorganic acid. In practice the use of the salt form amounts to use of the base form. The compounds are useful in both free base and salt form.

In addition, the following abbreviations stand for the following:

- "ACN" or "CH<sub>3</sub>CN" refers to acetonitrile.
- "Boc", "tBoc" or "Tboc" refers to t-butoxy carbonyl.
- 5 "DCC" refers to N,N'-dicyclohexylcarbodiimide.
- "Fmoc" refers to fluorenylmethoxycarbonyl.
- "HBTU" refers to 2-(1H-benzotriazol-1-yl)-1,1,3,3,-tetramethyluronium hexafluorophosphate.
- "HOBt" refers to 1-hydroxybenzotriazole monohydrate.
- 10 "homoP" or hPro" refers to homoproline.
- "MeAla" or "Nme" refers to N-methylalanine.
- "naph" refers to naphthylalanine.
- "pG" or pGly" refers to pentylglycine.
- "tBuG" refers to tertiary-butylglycine.
- 15 "ThioP" or tPro" refers to thioproline.
- 3Hyp" refers to 3-hydroxyproline
- 4Hyp" refers to 4-hydroxyproline
- NAG" refers to N-alkylglycine
- NAPG" refers to N-alkylpentylglycine
- 20 "Norval" refers to norvaline
- "Norleu" refers to norleucine

#### Preparation of Compounds

- 25 The exendins and exendin agonists described herein may be prepared using standard solid-phase peptide synthesis techniques and preferably an automated or semiautomated peptide synthesizer. Typically, using such

techniques, an  $\alpha$ -N-carbamoyl protected amino acid and an amino acid attached to the growing peptide chain on a resin are coupled at room temperature in an inert solvent such as dimethylformamide, N-methylpyrrolidinone or  
5 methylene chloride in the presence of coupling agents such as dicyclohexylcarbodiimide and 1-hydroxybenzotriazole in the presence of a base such as diisopropylethylamine. The  $\alpha$ -N-carbamoyl protecting group is removed from the resulting peptide-resin using a reagent such as  
10 trifluoroacetic acid or piperidine, and the coupling reaction repeated with the next desired N-protected amino acid to be added to the peptide chain. Suitable N-protecting groups are well known in the art, with t-butyloxycarbonyl (tBoc) and fluorenylmethoxycarbonyl  
15 (Fmoc) being preferred herein.

The solvents, amino acid derivatives and 4-methylbenzhydryl-amine resin used in the peptide synthesizer may be purchased from Applied Biosystems Inc. (Foster City, CA). The following side-chain protected  
20 amino acids may be purchased from Applied Biosystems, Inc.: Boc-Arg(Mts), Fmoc-Arg(Pmc), Boc-Thr(Bzl), Fmoc-Thr(t-Bu), Boc-Ser(Bzl), Fmoc-Ser(t-Bu), Boc-Tyr(BrZ), Fmoc-Tyr(t-Bu), Boc-Lys(Cl-Z), Fmoc-Lys(Boc), Boc-Glu(Bzl), Fmoc-Glu(t-Bu), Fmoc-His(Trt), Fmoc-  
25 Asn(Trt), and Fmoc-Gln(Trt). Boc-His(BOM) may be purchased from Applied Biosystems, Inc. or Bachem Inc. (Torrance, CA). Anisole, dimethylsulfide, phenol, ethanedithiol, and thioanisole may be obtained from

Aldrich Chemical Company (Milwaukee, WI). Air Products and Chemicals (Allentown, PA) supplies HF. Ethyl ether, acetic acid and methanol may be purchased from Fisher Scientific (Pittsburgh, PA).

5           Solid phase peptide synthesis may be carried out with an automatic peptide synthesizer (Model 430A, Applied Biosystems Inc., Foster City, CA) using the NMP/HOBt (Option 1) system and tBoc or Fmoc chemistry (see, Applied Biosystems User's Manual for the ABI 430A Peptide  
10       Synthesizer, Version 1.3B July 1, 1988, section 6, pp. 49-70, Applied Biosystems, Inc., Foster City, CA) with capping. Boc-peptide-resins may be cleaved with HF (-5° C to 0° C, 1 hour). The peptide may be extracted from the  
15       filtrates lyophilized. The Fmoc-peptide resins may be cleaved according to standard methods (Introduction to Cleavage Techniques, Applied Biosystems, Inc., 1990, pp. 6-12). Peptides may be also be assembled using an  
20       Advanced Chem Tech Synthesizer (Model MPS 350, Louisville, Kentucky).

          Peptides may be purified by RP-HPLC (preparative and analytical) using a Waters Delta Prep 3000 system. A C4, C8 or C18 preparative column (10 $\mu$  , 2.2 x 25 cm; Vydac, Hesperia, CA) may be used to isolate peptides, and purity  
25       may be determined using a C4, C8 or C18 analytical column (5 $\mu$  , 0.46 x 25 cm; Vydac). Solvents (A=0.1% TFA/water and B=0.1% TFA/CH<sub>3</sub>CN) may be delivered to the analytical column at a flowrate of 1.0 ml/min and to the preparative column at 15 ml/min. Amino acid analyses may be performed



on the Waters Pico Tag system and processed using the Maxima program. Peptides may be hydrolyzed by vapor-phase acid hydrolysis (115° C, 20-24 h). Hydrolysates may be derivatized and analyzed by standard methods (Cohen, et al., The Pico Tag Method: A Manual of Advanced Techniques for Amino Acid Analysis, pp. 11-52, Millipore Corporation, Milford, MA (1989)). Fast atom bombardment analysis may be carried out by M-Scan, Incorporated (West Chester, PA). Mass calibration may be performed using cesium iodide or cesium iodide/glycerol. Plasma desorption ionization analysis using time of flight detection may be carried out on an Applied Biosystems Bio-Ion 20 mass spectrometer. Electrospray mass spectroscopy may be carried out on a VG-Trio machine.

Peptide compounds useful in the invention may also be prepared using recombinant DNA techniques, using methods now known in the art. See, e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual, 2d Ed., Cold Spring Harbor (1989). Non-peptide compounds useful in the present invention may be prepared by art-known methods. For example, phosphate-containing amino acids and peptides containing such amino acids, may be prepared using methods known in the art. See, e.g., Bartlett and Landen, Biorg. Chem. 14:356-377 (1986).

The compounds described above are useful in view of their pharmacological properties. In particular, the compounds of the invention possess activity as agents to reduce food intake. They can be used to treat conditions or diseases which can be alleviated by reducing food

intake.

Compositions useful in the invention may conveniently be provided in the form of formulations suitable for parenteral (including intravenous, intramuscular and subcutaneous) or nasal or oral administration. In some cases, it will be convenient to provide an exendin or exendin agonist and another food-intake-reducing, plasma glucose-lowering or plasma lipid-lowering agent, such as amylin, an amylin agonist, a CCK, or a leptin, in a single composition or solution for administration together. In other cases, it may be more advantageous to administer the additional agent separately from said exendin or exendin agonist. A suitable administration format may best be determined by a medical practitioner for each patient individually. Suitable pharmaceutically acceptable carriers and their formulation are described in standard formulation treatises, e.g., Remington's Pharmaceutical Sciences by E.W. Martin. See also Wang, Y.J. and Hanson, M.A. "Parenteral Formulations of Proteins and Peptides: Stability and Stabilizers," Journal of Parenteral Science and Technology, Technical Report No. 10, Supp. 42:2S (1988).

Compounds useful in the invention can be provided as parenteral compositions for injection or infusion. They can, for example, be suspended in an inert oil, suitably a vegetable oil such as sesame, peanut, olive oil, or other acceptable carrier. Preferably, they are suspended in an aqueous carrier, for example, in an isotonic buffer solution at a pH of about 3.0 to 8.0, preferably at a pH of

about 3.5 to 5.0. These compositions may be sterilized by conventional sterilization techniques, or may be sterile filtered. The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions, such as pH buffering agents. Useful buffers include for example, sodium acetate/acetic acid buffers. A form of repository or "depot" slow release preparation may be used so that therapeutically effective amounts of the preparation are delivered into the bloodstream over many hours or days following transdermal injection or delivery.

The desired isotonicity may be accomplished using sodium chloride or other pharmaceutically acceptable agents such as dextrose, boric acid, sodium tartrate, propylene glycol, polyols (such as mannitol and sorbitol), or other inorganic or organic solutes. Sodium chloride is preferred particularly for buffers containing sodium ions.

The claimed compositions can also be formulated as pharmaceutically acceptable salts (e.g., acid addition salts) and/or complexes thereof. Pharmaceutically acceptable salts are non-toxic salts at the concentration at which they are administered. The preparation of such salts can facilitate the pharmacological use by altering the physical-chemical characteristics of the composition without preventing the composition from exerting its physiological effect. Examples of useful alterations in physical properties include lowering the melting point to facilitate transmucosal administration and increasing the solubility to facilitate the administration of higher

concentrations of the drug.

Pharmaceutically acceptable salts include acid addition salts such as those containing sulfate, hydrochloride, phosphate, sulfamate, acetate, citrate, lactate, tartrate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, cyclohexylsulfamate and quinate. Pharmaceutically acceptable salts can be obtained from acids such as hydrochloric acid, sulfuric acid, phosphoric acid, sulfamic acid, acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, cyclohexylsulfamic acid, and quinic acid. Such salts may be prepared by, for example, reacting the free acid or base forms of the product with one or more equivalents of the appropriate base or acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is then removed in vacuo or by freeze-drying or by exchanging the ions of an existing salt for another ion on a suitable ion exchange resin.

Carriers or excipients can also be used to facilitate administration of the compound. Examples of carriers and excipients include calcium carbonate, calcium phosphate, various sugars such as lactose, glucose, or sucrose, or types of starch, cellulose derivatives, gelatin, vegetable oils, polyethylene glycols and physiologically compatible solvents. The compositions or pharmaceutical composition can be administered by different routes including intravenously, intraperitoneal, subcutaneous, and intramuscular, orally, topically, transmucosally, or by

pulmonary inhalation.

If desired, solutions of the above compositions may be thickened with a thickening agent such as methyl cellulose.

They may be prepared in emulsified form, either water in oil or oil in water. Any of a wide variety of pharmaceutically acceptable emulsifying agents may be employed including, for example, acacia powder, a non-ionic surfactant (such as a Tween), or an ionic surfactant (such as alkali polyether alcohol sulfates or sulfonates, e.g., a Triton).

Compositions useful in the invention are prepared by mixing the ingredients following generally accepted procedures. For example, the selected components may be simply mixed in a blender or other standard device to produce a concentrated mixture which may then be adjusted to the final concentration and viscosity by the addition of water or thickening agent and possibly a buffer to control pH or an additional solute to control tonicity.

For use by the physician, the compositions will be provided in dosage unit form containing an amount of an exendin or exendin agonist, for example, exendin-3, and/or exendin-4, with or without another food intake-reducing, plasma glucose-lowering or plasma lipid-lowering agent. Therapeutically effective amounts of an exendin or exendin agonist for use in reducing food intake are those that suppress appetite at a desired level. As will be recognized by those in the field, an effective amount of therapeutic agent will vary with many factors including the age and weight of the patient, the patient's physical

condition, the blood sugar level and other factors.

The effective daily appetite-suppressing dose of the compounds will typically be in the range of about 10 to 30  $\mu\text{g}$  to about 5 mg/day, preferably about 10 to 30  $\mu\text{g}$  to about 2 mg/day and more preferably about 10 to 100  $\mu\text{g}$  to about 1 mg/day, most preferably about 30  $\mu\text{g}$  to about 500  $\mu\text{g}$ /day, for a 70 kg patient, administered in a single or divided doses. The exact dose to be administered is determined by the attending clinician and is dependent upon where the particular compound lies within the above quoted range, as well as upon the age, weight and condition of the individual. Administration should begin whenever the suppression of food intake, or weight lowering is desired, for example, at the first sign of symptoms or shortly after diagnosis of obesity, diabetes mellitus, or insulin-resistance syndrome. Administration may be by injection, preferably subcutaneous or intramuscular. Orally active compounds may be taken orally, however dosages should be increased 5-10 fold.

The optimal formulation and mode of administration of compounds of the present application to a patient depend on factors known in the art such as the particular disease or disorder, the desired effect, and the type of patient. While the compounds will typically be used to treat human subjects they may also be used to treat similar or identical diseases in other vertebrates such as other primates, farm animals such as swine, cattle and poultry, and sports animals and pets such as horses, dogs and cats.

To assist in understanding the present invention, the following Examples are included. The experiments relating to this invention should not, of course, be construed as specifically limiting the invention and such variations of the invention, now known or later developed, which would be within the purview of one skilled in the art are considered to fall within the scope of the invention as described herein and hereinafter claimed.

EXAMPLE 1: Exendin Injections Reduced the Food Intake of Normal Mice

All mice (NIH:Swiss mice) were housed in a stable environment of 22 ( $\pm$  2) $^{\circ}$  C, 60 ( $\pm$ 10) % humidity and a 12:12 light:dark cycle; with lights on at 0600. Mice were housed in groups of four in standard cages with *ad libitum* access to food (Teklad: LM 485; Madison, WI) and water except as noted, for at least two weeks before the experiments.

All experiments were conducted between the hours of 0700 and 0900. The mice were food deprived (food removed at 1600 hr from all animals on day prior to experiment) and individually housed. All mice received an intraperitoneal injection (5  $\mu$ l/kg) of either saline or exendin-4 at doses of 0.1, 1.0, 10 and 100  $\mu$ g/kg and were immediately presented with a pre-weighed food pellet (Teklad LM 485). The food pellet was weighed at 30-minute, 1-hr, 2-hr and 6-hr intervals to determine the amount of food eaten.

Figure 1 depicts cumulative food intake over periods of 0.5, 1, 2 and 6hr in overnight-fasted normal NIH:Swiss

mice following ip injection of saline, 2 doses of GLP-1, or 4 doses of exendin-4. At doses up to 100µg/kg, GLP-1 had no effect on food intake measured over any period, a result consistent with that previously reported (Bhavsar, S.P., et al., Soc. Neurosci. Abstr. 21:460 (188.8) (1995); and Turton, M.D., Nature, 379:69-72, (1996)).

In contrast, exendin-4 injections potently and dose-dependently inhibited food intake. The ED<sub>50</sub> for inhibition of food intake over 30 min was 1µg/kg, which is a level about as potent as amylin (ED<sub>50</sub> 3.6µg/kg) or the prototypical peripheral satiety agent, CCK (ED<sub>50</sub> 0.97µg/kg) as measured in this preparation. However, in contrast to the effects of amylin or CCK, which abate after 1-2 hours, the inhibition of food intake with exendin-4 was still present after at least 6 hours after injection.

#### EXAMPLE 2: Exendin Reduced the Food Intake of Obese Mice

All mice (female ob/ob mice) were housed in a stable environment of 22 (±2)° C, 60 (±10) % humidity and a 12:12 light:dark cycle; with lights on at 0600. Mice were housed in groups of four in standard cages with *ad libitum* access to food (Teklad: LM 485) and water except as noted, for at least two weeks before the experiments.

All experiments were conducted between the hours of 0700 and 0900. The mice were food deprived (food removed at 1600 hr from all animals on day prior to experiment) and individually housed. All mice received an intraperitoneal injection (5 µl/kg) of either saline or exendin-4 at doses



of 0.1, 1.0 and 10  $\mu\text{g/kg}$  (female ob/ob mice) and were immediately presented with a pre-weighed food pellet (Teklad LM 485). The food pellet was weighed at 30-minute, 1 -hr, 2-hr and 6-hr intervals to determine the amount of food eaten.

Figure 2 depicts the effect of exendin-4 in the ob/ob mouse model of obesity. The obese mice had a similar food intake-related response to exendin as the normal mice. Moreover, the obese mice were not hypersensitive to exendin, as has been observed with amylin and leptin (Young, A.A., et al., Program and Abstracts, 10th International Congress of Endocrinology, June 12-15, 1996 San Francisco, pg 419 (P2-58)).

### EXAMPLE 3: Intracerebroventricular Injections of Exendin

#### Inhibited Food Intake in Rats

All rats (Harlan Sprague-Dawley) were housed in a stable environment of 22 ( $\pm 2$ )° C, 60 ( $\pm 10$ )% humidity and a 12:12 light:dark cycle; with lights on at 0600. Rats were obtained from Zivic Miller with an intracerebroventricular cannula (ICV cannula) implanted (coordinates determined by actual weight of animals and referenced to Paxinos, G. and Watson, C. "The Rat Brain in stereotaxic coordinates," second edition. Academic Press) and were individually housed in standard cages with *ad libitum* access to food (Teklad: LM 485) and water for at least one week before the experiments.

All injections were given between the hours of 1700

and 1800. The rats were habituated to the ICV injection procedure at least once before the ICV administration of compound. All rats received an ICV injection (2  $\mu$ l/30 seconds) of either saline or exendin-4 at doses of 0.01, 0.03, 0.1, 0.3, and 1.0  $\mu$ g. All animals were then presented with pre-weighed food (Teklad LM 485) at 1800, when the lights were turned off. The amount of food left was weighed at 2-hr, 12-hr and 24-hr intervals to determine the amount of food eaten by each animal.

Figure 3 depicts a dose-dependent inhibition of food intake in rats that received doses greater than 0.1 $\mu$ g/rat. The ED<sub>50</sub> was  $\approx$  0.1 $\mu$ g, exendin-4 is thus  $\approx$ 100-fold more potent than intracerebroventricular injections of GLP-1 as reported by Turton, M.D., et al. (Nature 379:69-72 (1996)).

EXAMPLE 4: Exendin Agonists Reduced the Food Intake in Mice

All mice (NIH:Swiss mice) were housed in a stable environment of 22 ( $\pm$ 2)° C, 60 ( $\pm$ 10) % humidity and a 12:12 light:dark cycle; with lights on at 0600. Mice were housed in groups of four in standard cages with *ad libitum* access to food (Teklad: LM 485; Madison, WI) and water except as noted, for at least two weeks before the experiments.

All experiments were conducted between the hours of 0700 and 0900. The mice were food deprived (food removed at 1600 hr from all animals on day prior to experiment) and individually housed. All mice received an

intraperitoneal injection (5  $\mu$ l/kg) of either saline or test compound at doses of 1, 10, and 100  $\mu$ g/kg and immediately presented with a food pellet (Teklad LM 485).

The food pellet was weighed at 30-minute, 1-hr, 2-hr and  
5 6-hr intervals to determine the amount of food eaten.

Figure 4 depicts the cumulative food intake over periods of 0.5, 1, 2 and 6 hr in overnight-fasted normal NIH:Swiss mice following ip injection of saline or exendin-4 (1-30) ("Compound 1") in doses of 1, 10 and 100  
10  $\mu$ g/kg.

Figure 5 depicts the cumulative food intake over periods of 0.5, 1, 2 and 6 hr in overnight-fasted normal NIH:Swiss mice following ip injection of saline or exendin-4 (1-30) amide ("Compound 2") in doses of 1, 10  
15 and 100  $\mu$ g/kg.

Figure 6 depicts the cumulative food intake over periods of 0.5, 1, 2 and 6 hr in overnight-fasted normal NIH:Swiss mice following ip injection of saline or exendin-4 (1-28) amide ("Compound 3") in doses of 1, 10  
20 and 100  $\mu$ g/kg.

Figure 7 depicts the cumulative food intake over periods of 0.5, 1, 2 and 6 hr in overnight-fasted normal NIH:Swiss mice following ip injection of saline or <sup>14</sup>Leu, <sup>25</sup>Phe exendin-4 amide ("Compound 4") in doses of 1, 10  
25 and 100  $\mu$ g/kg.

Figure 8 depicts the cumulative food intake over periods of 0.5, 1, 2 and 6 hr in overnight-fasted normal NIH:Swiss mice following ip injection of saline or <sup>14</sup>Leu, <sup>25</sup>Phe exendin-4 (1-28) amide ("Compound 5") in doses

of 1, 10 and 100  $\mu\text{g/kg}$ .

Figure 9 depicts the cumulative food intake over periods of 0.5, 1, 2 and 6 hr in overnight-fasted normal NIH:Swiss mice following ip injection of saline or  $^{14}\text{Leu}$ ,  $^{22}\text{Ala}$ ,  $^{25}\text{Phe}$  exendin-4 (1-28) amide ("Compound 6") in doses of 1, 10 and 100  $\mu\text{g/kg}$ .

#### EXAMPLE 5

##### Preparation of amidated peptide having SEQ. ID. NO. 9

The above-identified peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.). In general, single-coupling cycles were used throughout the synthesis and Fast Moc (HBTU activation) chemistry was employed. However, at some positions coupling was less efficient than expected and double couplings were required. In particular, residues Asp<sub>9</sub>, Thr<sub>7</sub>, and Phe<sub>6</sub> all required double coupling. Deprotection (Fmoc group removal) of the growing peptide chain using piperidine was not always efficient. Double deprotection was required at positions Arg<sub>20</sub>, Val<sub>19</sub>, and Leu<sub>14</sub>. Final deprotection of the completed peptide resin was achieved using a mixture of triethylsilane (0.2 mL), ethanedithiol (0.2 mL), anisole (0.2 mL), water (0.2 mL) and trifluoroacetic acid (15 mL) according to standard methods (Introduction to Cleavage Techniques, Applied Biosystems, Inc.) The peptide was precipitated in ether/water (50 mL) and centrifuged. The

precipitate was reconstituted in glacial acetic acid and lyophilized. The lyophilized peptide was dissolved in water). Crude purity was about 55%.

5       Used in purification steps and analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).

      The solution containing peptide was applied to a preparative C-18 column and purified (10% to 40% Solvent B in Solvent A over 40 minutes). Purity of fractions was determined isocratically using a C-18 analytical column.

10       Pure fractions were pooled furnishing the above-identified peptide. Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 14.5 minutes. Electrospray Mass Spectrometry (M):

15       calculated 4131.7; found 4129.3.

#### EXAMPLE 6

##### Preparation of Peptide having SEQ. ID. NO. 10

20       The above-identified peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a

25       similar way to Example 5. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 25% to 75% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 21.5

minutes. Electrospray Mass Spectrometry (M): calculated 4168.6; found 4171.2.

#### EXAMPLE 7

##### 5      Preparation of Peptide having SEQ. ID. NO. 11

The above-identified peptide was assembled on 4-(2'-  
4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
10 Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 5. Used in analysis were Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
15 Solvent A over 30 minutes) of the lyophilized peptide gave  
product peptide having an observed retention time of 17.9  
minutes. Electrospray Mass Spectrometry (M): calculated  
4147.6; found 4150.2.

##### 20      EXAMPLE 8

##### Preparation of Peptide having SEQ. ID. NO. 12

The above-identified peptide was assembled on 4-(2'-  
4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
25 norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 5. Used in analysis were Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).

Analytical RP-HPLC (gradient 35% to 65% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 19.7 minutes. Electrospray Mass Spectrometry (M): calculated  
5 4212.6; found 4213.2.

#### EXAMPLE 9

##### Preparation of Peptide having SEQ. ID. NO. 13

10 The above-identified peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
15 similar way to Example 5. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 50% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave  
product peptide having an observed retention time of 16.3  
20 minutes. Electrospray Mass Spectrometry (M): calculated  
4262.7; found 4262.4.

#### EXAMPLE 10

##### Preparation of Peptide having SEQ. ID. NO. 14

25 The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.),

cleaved from the resin, deprotected and purified in a similar way to Example 5. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4172.6

10

EXAMPLE 11Preparation of Peptide having SEQ. ID. NO. 15

15

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 5. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4224.7.

25



EXAMPLE 12Preparation of Peptide having SEQ. ID. NO. 16

5           The above-identified peptide is assembled on 4-(2'-  
4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
10       similar way to Example 5. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
15       product peptide. Electrospray Mass Spectrometry (M):  
calculated 4172.6

EXAMPLE 13Preparation of Peptide having SEQ. ID. NO. 17

20           The above-identified peptide is assembled on 4-(2'-  
4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
25       cleaved from the resin, deprotected and purified in a  
similar way to Example 5. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is

then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4186.6

5

EXAMPLE 14Preparation of Peptide having SEQ. ID. NO. 18

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 5. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4200.7

20

EXAMPLE 15Preparation of Peptide having SEQ. ID. NO. 19

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 5. Used in analysis are Solvent A

(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
5 product peptide. Electrospray Mass Spectrometry (M):  
calculated 4200.7

#### EXAMPLE 16

##### Preparation of Peptide having SEQ. ID. NO. 20

10

The above-identified peptide is assembled on 4-(2'-  
4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
15 cleaved from the resin, deprotected and purified in a  
similar way to Example 5. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
20 then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 4202.7.

#### EXAMPLE 17

25

##### Preparation of Peptide having SEQ. ID. NO. 21

The above-identified peptide is assembled on 4-(2'-  
4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using

Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 5. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).

5 Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 4145.6.

10

#### EXAMPLE 18

##### Preparation of Peptide having SEQ. ID. NO. 22

The above-identified peptide is assembled on 4-(2'-  
15 4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 5. Used in analysis are Solvent A  
20 (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
25 calculated 4184.6.

EXAMPLE 19Preparation of Peptide having SEQ. ID. NO. 23

5           The above-identified peptide is assembled on 4-(2'-  
4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
10       similar way to Example 5. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
15       product peptide. Electrospray Mass Spectrometry (M):  
calculated 4145.6.

EXAMPLE 20

20       Preparation of Peptide having SEQ. ID. NO. 24

          The above-identified peptide is assembled on 4-(2'-  
4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
25       Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 5. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in

Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4224.7.

5

#### EXAMPLE 21

##### Preparation of Peptide having SEQ. ID. NO. 25

The above-identified peptide is assembled on 4-(2'-  
10 4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 5. Used in analysis are Solvent A  
15 (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
20 calculated 4172.6.

#### EXAMPLE 22

##### Preparation of Peptide having SEQ. ID. NO. 26

25 The above-identified peptide is assembled on 4-(2'-  
4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a

similar way to Example 5. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
5 then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 4115.5.

10

EXAMPLE 23Preparation of Peptide having SEQ. ID. NO. 27

The above-identified peptide is assembled on 4-(2'-  
4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
15 norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 5. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
20 Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 4188.6.

25

EXAMPLE 24Preparation of Peptide having SEQ. ID. NO. 28

5       The above-identified peptide is assembled on 4-(2'-  
4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 5. Used in analysis are Solvent A  
10       (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
15       calculated 4131.6.

EXAMPLE 25Preparation of Peptide having SEQ. ID. NO. 29

20       The above-identified peptide is assembled on 4-(2'-  
4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
25       similar way to Example 5. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the



product peptide. Electrospray Mass Spectrometry (M):  
calculated 4172.6.

#### EXAMPLE 26

##### 5      Preparation of Peptide having SEQ. ID. NO. 30

The above-identified peptide is assembled on 4-(2'-  
4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
10 Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 5. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
15 Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 4145.6.

20

#### EXAMPLE 27

##### Preparation of Peptide having SEQ. ID. NO. 31

The above-identified peptide is assembled on 4-(2'-  
4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
25 norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 5. Additional double couplings are  
required at the thioproline positions 38, 37, 36 and 31.

Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4266.8.

#### EXAMPLE 28

##### Preparation of Peptide having SEQ. ID. NO. 32

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 5. Additional double couplings are required at the thioproline positions 38, 37 and 36. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4246.8.

#### EXAMPLE 29

##### Preparation of Peptide having SEQ. ID. NO. 33

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide

norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 5. Additional double couplings are required at the homoproline positions 38, 37, 36 and 31. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4250.8.

#### EXAMPLE 30

##### Preparation of Peptide having SEQ. ID. NO. 34

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 5. Additional double couplings are required at the homoproline positions 38, 37, and 36. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4234.8.

EXAMPLE 31Preparation of Peptide having SEQ. ID. NO. 35

5           The above-identified peptide is assembled on 4-(2'-  
4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
10 similar way to Example 5. Additional double couplings are  
required at the thioproline positions 38, 37, 36 and 31.  
Used in analysis are Solvent A (0.1% TFA in water) and  
Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient  
30% to 60% Solvent B in Solvent A over 30 minutes) of the  
15 lyophilized peptide is then carried out to determine the  
retention time of the product peptide. Electrospray Mass  
Spectrometry (M): calculated 4209.8.

EXAMPLE 32

20           Preparation of Peptide having SEQ. ID. NO. 36

          The above-identified peptide is assembled on 4-(2'-  
4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
25 Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 5. Additional double couplings are  
required at the homoproline positions 38, 37, 36 and 31.  
Used in analysis are Solvent A (0.1% TFA in water) and

Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4193.7.

### EXAMPLE 33

#### Preparation of Peptide having SEQ. ID. NO. 37

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 5. Additional double couplings are required at the N-methylalanine positions 38, 37, 36 and 31. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3858.2.

### EXAMPLE 34

#### Preparation of Peptide having SEQ. ID. NO. 38

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using

Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 5. Additional double couplings are  
required at the N-methylalanine positions 38, 37 and 36.

5 Used in analysis are Solvent A (0.1% TFA in water) and  
Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient  
30% to 60% Solvent B in Solvent A over 30 minutes) of the  
lyophilized peptide is then carried out to determine the  
retention time of the product peptide. Electrospray Mass  
10 Spectrometry (M): calculated 3940.3.

#### EXAMPLE 35

##### Preparation of Peptide having SEQ. ID. NO. 39

15

The above-identified peptide is assembled on 4-(2'-  
4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
20 cleaved from the resin, deprotected and purified in a  
similar way to Example 5. Additional double couplings are  
required at the N-methylalanine positions 38, 37, 36 and  
31. Used in analysis are Solvent A (0.1% TFA in water) and  
Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient  
25 30% to 60% Solvent B in Solvent A over 30 minutes) of the  
lyophilized peptide is then carried out to determine the  
retention time of the product peptide. Electrospray Mass  
Spectrometry (M): calculated 3801.1.

EXAMPLE 36

Preparation of C-terminal carboxylic acid Peptides  
corresponding to the above C-terminal amide sequences.

5

The above peptides of Examples 5 to 35 are assembled on the so called Wang resin (p-alkoxybenzylalcohol resin (Bachem, 0.54 mmole/g)) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin,  
10 deprotected and purified in a similar way to Example 5. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the  
15 retention time of the product peptide. Electrospray Mass Spectrometry provides an experimentally determined (M).

EXAMPLE 37

20

Preparation of Peptide having SEQ ID NO. 7

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn  
Gly Gly-NH<sub>2</sub> [SEQ. ID. NO. 7]

25

The above amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.). In  
30 general, single-coupling cycles were used throughout the

synthesis and Fast Moc (HBTU activation) chemistry was employed. Deprotection (Fmoc group removal) of the growing peptide chain was achieved using piperidine. Final deprotection of the completed peptide resin was achieved using a mixture of triethylsilane (0.2 mL), ethanedithiol (0.2 mL), anisole (0.2 mL), water (0.2 mL) and trifluoroacetic acid (15 mL) according to standard methods (Introduction to Cleavage Techniques, Applied Biosystems, Inc.) The peptide was precipitated in ether/water (50 mL) and centrifuged. The precipitate was reconstituted in glacial acetic acid and lyophilized. The lyophilized peptide was dissolved in water). Crude purity was about 75%.

Used in purification steps and analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). The solution containing peptide was applied to a preparative C-18 column and purified (10% to 40% Solvent B in Solvent A over 40 minutes). Purity of fractions was determined isocratically using a C-18 analytical column. Pure fractions were pooled furnishing the above-identified peptide. Analytical RP-HPLC (gradient 30% to 50% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 18.9 minutes. Electrospray Mass Spectrometry (M): calculated 3408.0; found 3408.9.



EXAMPLE 38Preparation of Peptide having SEQ ID NO. 40

5 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 40]

The above amidated peptide was assembled on 4-(2'-4'-  
10 dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 37. Used in analysis were Solvent A  
15 (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 40% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide gave  
product peptide having an observed retention time of 17.9  
minutes. Electrospray Mass Spectrometry (M): calculated  
20 3294.7; found 3294.8.

EXAMPLE 39Preparation of Peptide having SEQ ID NO. 41

25

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 41]

The above-identified amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 29% to 36% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 20.7 minutes. Electrospray Mass Spectrometry (M): calculated 3237.6; found 3240.

15

EXAMPLE 40Preparation of Peptide having SEQ ID NO. 42

His Ala Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 42]

20

The above amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).

25

Analytical RP-HPLC (gradient 36% to 46% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 15.2 minutes. Electrospray Mass Spectrometry (M): calculated  
5 3251.6; found 3251.5.

#### EXAMPLE 41

##### Preparation of Peptide having SEQ ID NO. 43

10 His Gly Glu Gly Ala Phe Thr Ser Asp Leu Ser Lys Gln  
Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys  
Asn-NH<sub>2</sub> [SEQ. ID. NO. 43]

The above amidated peptide was assembled on 4-(2'-4'-  
15 dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 37. Used in analysis were Solvent A  
20 (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 36% to 46% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide gave  
product peptide having an observed retention time of 13.1  
minutes. Electrospray Mass Spectrometry (M): calculated  
25 3207.6; found 3208.3.

EXAMPLE 42Preparation of Peptide having SEQ ID NO. 44

His Gly Glu Gly Thr Ala Thr Ser Asp Leu Ser Lys Gln Leu  
5 Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 44]

The above amidated peptide was assembled on 4-(2'-4'-  
dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
10 norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 37. Used in analysis were Solvent  
A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
15 Analytical RP-HPLC (gradient 35% to 45% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide gave  
product peptide having an observed retention time of 12.8  
minutes. Electrospray Mass Spectrometry (M): calculated  
3161.5; found 3163.

20

EXAMPLE 43Preparation of Peptide having SEQ ID NO. 45

His Gly Glu Gly Thr Phe Thr Ala Asp Leu Ser Lys Gln Leu  
25 Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 45]

The above-identified amidated peptide was assembled

on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
5 purified in a similar way to Example 37. Used in analysis  
were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 36% to 46% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
gave product peptide having an observed retention time of  
10 15.2 minutes. Electrospray Mass Spectrometry (M):  
calculated 3221.6; found 3222.7.

#### EXAMPLE 44

##### Preparation of Peptide having SEQ ID NO. 46

15

His Gly Glu Gly Thr Phe Thr Ser Asp Ala Ser Lys Gln Leu  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 46]

20

The above-identified amidated peptide was assembled  
on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
25 purified in a similar way to Example 37. Used in analysis  
were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 34% to 44% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide

gave product peptide having an observed retention time of 14.3 minutes. Electrospray Mass Spectrometry (M): calculated 3195.5; found 3199.4.

5

EXAMPLE 45Preparation of Peptide having SEQ ID NO. 47

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ala Lys Gln Leu  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 47]

10

The above-identified amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 38% to 48% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 15.7 minutes. Electrospray Mass Spectrometry (M): calculated 3221.6; found 3221.6.

15

20

25

EXAMPLE 46Preparation of Peptide having SEQ ID NO. 48

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Ala Gln Leu  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 48]

30

The above-identified amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 38% to 48% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 18.1 minutes. Electrospray Mass Spectrometry (M): calculated 3180.5; found 3180.9.

#### EXAMPLE 47

##### Preparation of Peptide having SEQ ID NO. 49

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Ala Leu  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 49]

The above-identified amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Compound 1. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 36% to 46% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide

gave product peptide having an observed retention time of 17.0 minutes. Electrospray Mass Spectrometry (M): calculated 3180.6; found 3182.8.

5

EXAMPLE 48Preparation of Peptide having SEQ ID NO. 50

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Ala  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
10 [SEQ. ID. NO. 50]

The above-identified amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55  
15 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 32% to 42% Solvent B  
20 in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 14.9 minutes. Electrospray Mass Spectrometry (M): calculated 3195.5; found 3195.9.

25

EXAMPLE 49Preparation of Peptide having SEQ ID NO. 51

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu



Ala Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 51]

5 The above-identified amidated peptide was assembled  
on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
10 purified in a similar way to Example 37. Used in analysis  
were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 37% to 47% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
gave product peptide having an observed retention time of  
17.9 minutes. Electrospray Mass Spectrometry (M):  
15 calculated 3179.6; found 3179.0.

#### EXAMPLE 50

##### Preparation of Peptide having SEQ ID NO. 52

20

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
Glu Ala Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 52]

25

The above-identified amidated peptide was assembled  
on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and

purified in a similar way to Example 37. Used in analysis  
were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 37% to 47% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
5 gave product peptide having an observed retention time of  
14.3 minutes. Electrospray Mass Spectrometry (M):  
calculated 3179.6; found 3180.0.

#### EXAMPLE 51

10

##### Preparation of Peptide having SEQ ID NO. 53

15

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
Glu Glu Ala Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 53]

20

25

The above-identified peptide was assembled on 4-(2'-  
4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 37. Used in analysis were Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 37% to 47% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide gave  
product peptide having an observed retention time of 13.7  
minutes. Electrospray Mass Spectrometry (M): calculated  
3179.6; found 3179.0.

30

EXAMPLE 52Preparation of Peptide having SEQ ID NO. 54

5 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
Glu Glu Glu Ala Ala Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 54]

The above-identified amidated peptide was assembled  
10 on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
purified in a similar way to Example 37. Used in analysis  
15 were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 35% to 45% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
gave product peptide having an observed retention time of  
14.0 minutes. Electrospray Mass Spectrometry (M):  
20 calculated 3209.6; found 3212.8.

EXAMPLE 53Preparation of Peptide having SEQ ID NO. 55

25 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
Glu Glu Glu Ala Val Ala Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 55]

The above-identified amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 38% to 48% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 14.3 minutes. Electrospray Mass Spectrometry (M): calculated 3152.5; found 3153.5.

#### EXAMPLE 54

##### Preparation of Peptide having SEQ ID NO. 56

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
Glu Glu Glu Ala Val Arg Ala Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 56]

The above-identified amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 35% to 45% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide

gave product peptide having an observed retention time of 12.1 minutes. Electrospray Mass Spectrometry (M): calculated 3195.5; found 3197.7.

5

EXAMPLE 55Preparation of Peptide having SEQ ID NO. 57

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
Glu Glu Glu Ala Val Arg Leu Phe Ile Ala Phe Leu Lys Asn-NH<sub>2</sub>  
10 [SEQ. ID. NO. 57]

The above-identified amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55  
15 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 38% to 48% Solvent B  
20 in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 10.9 minutes. Electrospray Mass Spectrometry (M): calculated 3179.6; found 3180.5.

25

EXAMPLE 56Preparation of Peptide having SEQ ID NO. 58

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Ala Leu Lys Asn-NH<sub>2</sub>

[SEQ. ID. NO. 58]

The above-identified amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 32% to 42% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 17.5 minutes. Electrospray Mass Spectrometry (M): calculated 3161.5; found 3163.0.

#### EXAMPLE 57

##### Preparation of Peptide having SEQ ID NO. 59

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Ala Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 59]

The above-identified amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 32% to 42% Solvent B

in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 19.5 minutes. Electrospray Mass Spectrometry (M): calculated 3195.5; found 3199.

5

EXAMPLE 58Preparation of Peptide having SEQ ID NO. 60

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
10 Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Ala Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 60]

The above-identified amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
15 acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
20 in ACN). Analytical RP-HPLC (gradient 38% to 48% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 14.5 minutes. Electrospray Mass Spectrometry (M): calculated 3180.5; found 3183.7.

25

EXAMPLE 59Preparation of Peptide having SEQ ID NO. 61

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
5 Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Ala-NH<sub>2</sub>  
[SEQ. ID. NO. 61]

The above-identified amidated peptide was assembled  
on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
10 acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
purified in a similar way to Example 37. Used in analysis  
15 were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 34% to 44% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
gave product peptide having an observed retention time of  
22.8 minutes. Electrospray Mass Spectrometry (M):  
calculated 3194.6; found 3197.6.

20

EXAMPLE 60Preparation of Peptide having SEQ ID NO. 62

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
25 Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn  
Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro-NH<sub>2</sub> [SEQ. ID. NO.  
62]



The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4099.6.

#### EXAMPLE 61

#### Preparation of Peptide having SEQ ID NO. 63

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn  
Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro-NH<sub>2</sub> [SEQ. ID. NO.  
63]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA

in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M):  
5 calculated 4042.5.

## EXAMPLE 62

### Preparation of Peptide having SEQ ID NO. 64

10 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn  
Gly Gly Pro Ser Ser Gly Ala Pro Pro-NH<sub>2</sub> [SEQ. ID. NO. 64]

The above-identified peptide is assembled on 4-(2'-  
15 4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 37. Used in analysis are Solvent A  
20 (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
25 calculated 4002.4

EXAMPLE 63Preparation of Peptide having SEQ ID NO. 65

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
5 Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn  
Gly Gly Pro Ser Ser Gly Ala Pro Pro-NH<sub>2</sub> [SEQ. ID. NO. 65]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
10 acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
purified in a similar way to Example 37. Used in analysis  
15 are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3945.4.

20

EXAMPLE 64Preparation of Peptide having SEQ ID NO. 66

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln  
25 Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys  
Asn Gly Gly Pro Ser Ser Gly Ala Pro-NH<sub>2</sub> [SEQ. ID. NO. 66]

The above-identified amidated peptide is assembled on

4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
5 purified in a similar way to Example 37. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
10 product peptide. Electrospray Mass Spectrometry (M):  
calculated 3905.3.

#### EXAMPLE 65

##### Preparation of Peptide having SEQ ID NO. 67

15

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn  
Gly Gly Pro Ser Ser Gly Ala Pro-NH<sub>2</sub> [SEQ. ID. NO. 67]

20

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
25 purified in a similar way to Example 37. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide

is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3848.2.

5

EXAMPLE 66Preparation of Peptide having SEQ ID NO. 68

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn  
10 Gly Gly Pro Ser Ser Gly Ala-NH<sub>2</sub> [SEQ. ID. NO. 68]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55  
15 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
20 in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3808.2.

25

EXAMPLE 67Preparation of Peptide having SEQ ID NO. 69

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
5 Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn  
Gly Gly Pro Ser Ser Gly Ala-NH<sub>2</sub> [SEQ. ID. NO. 69]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
10 acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
purified in a similar way to Example 37. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
15 in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3751.1.

20

EXAMPLE 68Preparation of Peptide having SEQ ID NO. 70

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
25 Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn  
Gly Gly Pro Ser Ser Gly-NH<sub>2</sub> [SEQ. ID. NO. 70]

The above-identified amidated peptide is assembled on

4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
5 purified in a similar way to Example 37. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
10 product peptide. Electrospray Mass Spectrometry (M):  
calculated 3737.1.

#### EXAMPLE 69

##### Preparation of Peptide having SEQ ID NO. 71

15

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn  
Gly Gly Pro Ser Ser Gly-NH<sub>2</sub> [SEQ. ID. NO. 71]

20

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
25 purified in a similar way to Example 37. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide

is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3680.1.

5

EXAMPLE 70Preparation of Peptide having SEQ ID NO. 72

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn  
10 Gly Gly Pro Ser Ser-NH<sub>2</sub> [SEQ. ID. NO. 72]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55  
15 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
20 in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3680.1

25

EXAMPLE 71Preparation of Peptide having SEQ ID NO. 73

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
30 Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn  
Gly Gly Pro Ser Ser-NH<sub>2</sub> [SEQ. ID. NO. 73]



The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3623.0.

15

EXAMPLE 72Preparation of Peptide having SEQ ID NO. 74

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn  
20 Gly Gly Pro Ser-NH<sub>2</sub> [SEQ. ID. NO. 74]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA

in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M):  
5 calculated 3593.0

### EXAMPLE 73

#### Preparation of Peptide having SEQ ID NO. 75

10 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn  
Gly Gly Pro Ser-NH<sub>2</sub> [SEQ. ID. NO. 75]

The above-identified amidated peptide is assembled on  
15 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
purified in a similar way to Example 37. Used in analysis  
20 are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
25 calculated 3535.9

EXAMPLE 74Preparation of Peptide having SEQ ID NO. 76

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
5 Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn  
Gly Gly Pro-NH<sub>2</sub> [SEQ. ID. NO. 76]

The above-identified peptide is assembled on 4-(2'-  
4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
10 norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 37. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
15 Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3505.9.

20

EXAMPLE 75Preparation of Peptide having SEQ ID NO. 77

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
25 Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn  
Gly Gly Pro-NH<sub>2</sub> [SEQ. ID. NO. 77]

The above-identified amidated peptide is assembled on

4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
5 purified in a similar way to Example 37. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
10 product peptide. Electrospray Mass Spectrometry (M):  
calculated 3448.8.

#### EXAMPLE 76

##### Preparation of Peptide having SEQ ID NO. 78

15

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn  
Gly Gly-NH<sub>2</sub> [SEQ. ID. NO. 78]

20

The above-identified peptide is assembled on 4-(2'-  
4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
25 similar way to Example 37. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is

then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3351.7.

5

EXAMPLE 77

Preparation of Peptide having SEQ ID NO. 79

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
10 Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn  
Gly-NH<sub>2</sub> [SEQ. ID. NO. 79]

The above-identified peptide is assembled on 4-(2'-  
4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
15 norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 37. Used in analysis are Solvent A  
(0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
20 Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3351.8.

25

EXAMPLE 78Preparation of Peptide having SEQ ID NO. 80

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
5 Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn  
Gly-NH<sub>2</sub> [SEQ. ID. NO. 80]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
10 acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
purified in a similar way to Example 37. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
15 in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3294.7.

20

EXAMPLE 79Preparation of Peptide having SEQ ID NO. 81

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
25 Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn  
Gly Gly tPro Ser Ser Gly Ala tPro tPro tPro-NH<sub>2</sub> [SEQ. ID.  
NO. 81]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Double couplings are required at residues 37,36 and 31. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4197.1.

15

EXAMPLE 80Preparation of Peptide having SEQ ID NO. 82

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn  
20 Gly Gly Pro Ser Ser Gly Ala tPro tPro tPro-NH<sub>2</sub> [SEQ. ID.  
NO. 82]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Double couplings

are required at residues 37, 36 and 31. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4179.1.

#### EXAMPLE 81

#### 10      Preparation of Peptide having SEQ ID NO. 83

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn  
Gly Gly NMeala Ser Ser Gly Ala Pro Pro-NH<sub>2</sub> [SEQ. ID. NO.  
15      83]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Double couplings are required at residues 36 and 31. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M):



calculated 3948.3.

EXAMPLE 82

Preparation of Peptide having SEQ ID NO. 84

5

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn  
Gly Gly NMeala Ser Ser Gly Ala NMeala Nmeala-NH<sub>2</sub> [SEQ. ID.  
NO. 84]

10

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
15 Biosystems, Inc.), cleaved from the resin, deprotected and  
purified in a similar way to Example 37. Double couplings  
are required at residues 36 and 31. Used in analysis are  
Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in  
ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
20 Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3840.1.

EXAMPLE 83Preparation of Peptide having SEQ ID NO. 85

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
5 Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn  
Gly Gly hPro Ser Ser Gly Ala hPro hPro-NH<sub>2</sub> [SEQ. ID. NO.  
85]

The above-identified amidated peptide is assembled on  
10 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
purified in a similar way to Example 37. Double couplings  
15 are required at residues 36 and 31. Used in analysis are  
Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in  
ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
20 product peptide. Electrospray Mass Spectrometry (M):  
calculated 4050.1.

EXAMPLE 84Preparation of Peptide having SEQ ID NO. 86

25 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn  
Gly Gly hPro Ser Ser Gly Ala hPro-NH<sub>2</sub> [SEQ. ID. NO. 86]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. A double coupling is required at residue 31. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3937.1

15

#### EXAMPLE 85

##### Preparation of Peptide having SEQ ID NO. 87

Arg Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
20 Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn  
Gly Gly Pro Ser Ser Gly Ala-NH<sub>2</sub> [SEQ. ID. NO. 87]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis

are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M):  
5 calculated 3827.2.

#### EXAMPLE 86

##### Preparation of Peptide having SEQ ID NO. 88

10

His Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn  
Gly Gly-NH<sub>2</sub> [SEQ. ID. NO. 88]

15

20

25

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M):  
calculated 3394.8.

EXAMPLE 87Preparation of Peptide having SEQ ID NO. 89

His Gly Glu Gly Thr Naphthylala Thr Ser Asp Leu Ser Lys  
5 Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu  
Lys Asn-NH<sub>2</sub> [SEQ. ID. NO. 89]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
10 acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
purified in a similar way to Example 37. Used in analysis  
15 are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3289.5.

20

EXAMPLE 88Preparation of Peptide having SEQ ID NO. 90

His Gly Glu Gly Thr Phe Ser Ser Asp Leu Ser Lys Gln Met  
25 Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 90]

The above-identified amidated peptide is assembled on

4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
5 purified in a similar way to Example 37. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
10 product peptide. Electrospray Mass Spectrometry (M):  
calculated 3280.7.

#### EXAMPLE 89

##### Preparation of Peptide having SEQ ID NO. 91

15

His Gly Glu Gly Thr Phe Ser Thr Asp Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 91]

20

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
25 purified in a similar way to Example 37. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide

is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3294.7.

5

EXAMPLE 90Preparation of Peptide having SEQ ID NO. 92

His Gly Glu Gly Thr Phe Thr Ser Glu Leu Ser Lys Gln Met  
Ala Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 92]

10

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3250.7.

15

20

EXAMPLE 91

25

Preparation of Peptide having SEQ ID NO. 93

His Gly Glu Gly Thr Phe Thr Ser Asp pentylgly Ser Lys Gln  
Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys

Asn-NH<sub>2</sub> [SEQ. ID. NO. 93]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3253.5.

#### EXAMPLE 92

##### Preparation of Peptide having SEQ ID NO. 94

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
Glu Glu Glu Ala Val Arg Leu Naphthylala Ile Glu Phe Leu  
Lys Asn-NH<sub>2</sub> [SEQ. ID. NO. 94]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis



are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3289.5.

### EXAMPLE 93

#### Preparation of Peptide having SEQ ID NO. 95

10

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe tButylgly Glu Trp Leu Lys  
Asn-NH<sub>2</sub> [SEQ. ID. NO. 95]

15

20

25

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3183.4.

EXAMPLE 94Preparation of Peptide having SEQ ID NO. 96

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
5 Glu Glu Glu Ala Val Arg Leu Phe Ile Asp Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 96]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
10 acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
purified in a similar way to Example 37. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
15 in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3237.6.

20

EXAMPLE 95Preparation of Peptide having SEQ ID NO. 97

His Gly Glu Gly Thr Phe Thr Ser Asp Ala Ser Lys Gln Leu  
25 Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn  
Gly Gly Pro Ser Ser-NH<sub>2</sub> [SEQ. ID. NO. 97]

The above-identified amidated peptide is assembled on

4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
5 purified in a similar way to Example 37. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
10 product peptide. Electrospray Mass Spectrometry (M):  
calculated 3637.9.

#### EXAMPLE 96

##### Preparation of Peptide having SEQ ID NO. 98

15

His Gly Glu Gly Thr Phe Thr Ser Asp Ala Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn  
Gly-NH<sub>2</sub> [SEQ. ID. NO. 98]

20

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
25 purified in a similar way to Example 37. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide

is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3309.7.

5

EXAMPLE 97Preparation of Peptide having SEQ ID NO. 99

His Gly Glu Gly Thr Phe Thr Ser Asp Ala Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn  
10 Gly Gly hPro Ser Ser Gly Ala hPro hPro-NH<sub>2</sub> [SEQ. ID. NO.  
99]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
15 acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
purified in a similar way to Example 37. Double couplings  
are required at residues 36 and 31. Used in analysis are  
20 Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in  
ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide is  
then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
25 calculated 3711.1.

EXAMPLE 98

Preparation of C-terminal carboxylic acid peptides  
corresponding to the above C-terminal amide sequences for  
SEQ ID NOS. 7, 40-61, 68-75, 78-80 and 87-96

5

Peptides having the sequences of SEQ ID NOS. 7, 40-61, 68-75, 78-80 and 87-96 are assembled on the so called Wang resin (p-alkoxybenzylalcohol resin (Bachem, 0.54 mmole/g)) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry provides an experimentally determined (M).

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EXAMPLE 99

Preparation of C-terminal carboxylic acid peptides  
corresponding to the above C-terminal amide sequences for  
SEQ ID NOS. 62-67, 76, 77 and 81-86

25

Peptides having the sequences of SEQ ID NOS. 62-67, 76, 77 and 81-86 are assembled on the 2-chlorotritylchloride resin (200-400 mesh), 2% DVB (Novabiochem, 0.4-1.0 mmole/g)) using Fmoc-protected amino

acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry provides an experimentally determined (M).

10

EXAMPLE 100Preparation of Peptide having SEQ ID NO. 100

Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 100]

15

The above amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.). In general, single-coupling cycles were used throughout the synthesis and Fast Moc (HBTU activation) chemistry was employed. Deprotection (Fmoc group removal) of the growing peptide chain was achieved using piperidine. Final deprotection of the completed peptide resin was achieved using a mixture of triethylsilane (0.2 mL), ethanedithiol (0.2 mL), anisole (0.2 mL), water (0.2 mL) and trifluoroacetic acid (15 mL) according to standard methods (Introduction to Cleavage Techniques, Applied Biosystems,

20

25

Inc.) The peptide was precipitated in ether/water (50 mL) and centrifuged. The precipitate was reconstituted in glacial acetic acid and lyophilized. The lyophilized peptide was dissolved in water). Crude purity was about 75%.

Used in purification steps and analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).

The solution containing peptide was applied to a preparative C-18 column and purified (10% to 40% Solvent B in Solvent A over 40 minutes). Purity of fractions was determined isocratically using a C-18 analytical column. Pure fractions were pooled furnishing the above-identified peptide. Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 19.2 minutes. Electrospray Mass Spectrometry (M): calculated 3171.6; found 3172.

#### EXAMPLE 101

##### Preparation of Peptide having SEQ ID NO. 101

His Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 101]

The above amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.),

cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 36% to 46% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 14.9 minutes. Electrospray Mass Spectrometry (M): calculated 3179.6; found 3180.

10

EXAMPLE 102Preparation of Peptide having SEQ ID NO. 102

15

His Gly Glu Ala Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 102]

20

25

The above amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 37% to 47% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 12.2 minutes. Electrospray Mass Spectrometry (M): calculated 3251.6; found 3253.3.



EXAMPLE 103Preparation of Peptide having SEQ ID NO. 103

5 His Gly Glu Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Leu  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 103]

The above amidated peptide was assembled on 4-(2'-4'-  
10 dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide  
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using  
Fmoc-protected amino acids (Applied Biosystems, Inc.),  
cleaved from the resin, deprotected and purified in a  
similar way to Example 100. Used in analysis were Solvent  
15 A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).  
Analytical RP-HPLC (gradient 35% to 45% Solvent B in  
Solvent A over 30 minutes) of the lyophilized peptide gave  
product peptide having an observed retention time of 16.3  
minutes. Electrospray Mass Spectrometry (M): calculated  
20 3193.6; found 3197.

EXAMPLE 104Preparation of Peptide having SEQ ID NO. 104

25 Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 104]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3228.6.

#### EXAMPLE 105

##### Preparation of Peptide having SEQ ID NO. 105

His Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 105]

20

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide

is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3234.7.

5

EXAMPLE 106Preparation of Peptide having SEQ ID NO. 106

His Gly Glu Ala Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 106]

10

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3308.7.

15

20

25

EXAMPLE 107Preparation of Peptide having SEQ ID NO. 107

His Gly Glu Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>

[SEQ. ID. NO. 107]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3250.7

#### EXAMPLE 108

##### Preparation of Peptide having SEQ ID NO. 108

His Gly Glu Gly Thr Phe Thr Ser Asp Ala Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 108]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA

in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M):

5 calculated 3252.6.

#### EXAMPLE 109

##### Preparation of Peptide having SEQ ID NO. 109

10 Ala Ala Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 109]

The above-identified amidated peptide is assembled on  
15 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
purified in a similar way to Example 100. Used in analysis  
20 are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
25 calculated 3200.6.

EXAMPLE 110Preparation of Peptide having SEQ ID NO. 110

Ala Ala Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
5 [SEQ. ID. NO. 110]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
10 mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
purified in a similar way to Example 100. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
15 in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3143.5.

20

EXAMPLE 111Preparation of Peptide having SEQ ID NO. 111

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
25 Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 111]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy

acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis  
5 are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M):  
10 calculated 3214.6.

#### EXAMPLE 112

##### Preparation of Peptide having SEQ ID NO. 112

15 Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 112]

The above-identified amidated peptide is assembled on  
20 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis  
25 are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M):

calculated 3157.5.

EXAMPLE 113

Preparation of Peptide having SEQ ID NO. 113

5

Ala Gly Asp Gly Ala Phe Thr Ser Asp Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 113]

10

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
15 purified in a similar way to Example 100. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
20 product peptide. Electrospray Mass Spectrometry (M):  
calculated 3184.6.

EXAMPLE 114

Preparation of Peptide having SEQ ID NO. 114

25

Ala Gly Asp Gly Ala Phe Thr Ser Asp Leu Ser Lys Gln Leu  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 114]



The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3127.5.

15

EXAMPLE 115Preparation of Peptide having SEQ ID NO. 115

Ala Gly Asp Gly Thr NaphthylAla Thr Ser Asp Leu Ser Lys  
Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu  
Lys Asn-NH<sub>2</sub> [SEQ. ID. NO. 115]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B

in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3266.4.

5

#### EXAMPLE 116

##### Preparation of Peptide having SEQ ID NO. 116

Ala Gly Asp Gly Thr Naphthylala Thr Ser Asp Leu Ser Lys  
10 Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu  
Lys Asn-NH<sub>2</sub> [SEQ. ID. NO. 116]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
15 acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
20 in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3209.4.

25

#### EXAMPLE 117

##### Preparation of Peptide having SEQ ID NO. 117

Ala Gly Asp Gly Thr Phe Ser Ser Asp Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 117]

5           The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
10       purified in a similar way to Example 100. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
15       product peptide. Electrospray Mass Spectrometry (M):  
calculated 3200.6.

#### EXAMPLE 118

##### Preparation of Peptide having SEQ ID NO. 118

20

Ala Gly Asp Gly Thr Phe Ser Ser Asp Leu Ser Lys Gln Leu  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 118]

25           The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and

purified in a similar way to Example 100. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
5 is then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3143.5.

#### EXAMPLE 119

#### 10 Preparation of Peptide having SEQ ID NO. 119

Ala Gly Asp Gly Thr Phe Thr Ala Asp Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 119]

15

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
20 Biosystems, Inc.), cleaved from the resin, deprotected and  
purified in a similar way to Example 100. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
25 is then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3198.6.

EXAMPLE 120Preparation of Peptide having SEQ ID NO. 120

Ala Gly Asp Gly Thr Phe Thr Ala Asp Leu Ser Lys Gln Leu  
5 Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 120]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
10 acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
purified in a similar way to Example 100. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
15 in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3141.5.

20

EXAMPLE 121Preparation of Peptide having SEQ ID NO. 121

Ala Gly Asp Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Met  
25 Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 121]

The above-identified peptide is assembled on 4-(2'-  
4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide

norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3170.6.

#### EXAMPLE 122

##### Preparation of Peptide having SEQ ID NO. 122

Ala Gly Asp Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Leu  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 122]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M):

calculated 3113.5.

EXAMPLE 123

Preparation of Peptide having SEQ ID NO. 123

5

Ala Gly Asp Gly Thr Phe Thr Ser Glu Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 123]

10

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
15 purified in a similar way to Example 100. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
20 product peptide. Electrospray Mass Spectrometry (M):  
calculated 3228.6.

EXAMPLE 124

Preparation of Peptide having SEQ ID NO. 124

25

Ala Gly Asp Gly Thr Phe Thr Ser Glu Leu Ser Lys Gln Leu  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 124]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3171.6.

#### EXAMPLE 125

##### Preparation of Peptide having SEQ ID NO. 125

Ala Gly Asp Gly Thr Phe Thr Ser Asp Ala Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 125]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B



in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3172.5.

5

EXAMPLE 126

Preparation of Peptide having SEQ ID NO. 126

Ala Gly Asp Gly Thr Phe Thr Ser Asp Ala Ser Lys Gln Leu  
10 Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 126]

The above-identified amidated peptiden is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
15 acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis  
20 are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3115.4.

25

EXAMPLE 127Preparation of Peptide having SEQ ID NO. 127

Ala Gly Asp Gly Thr Phe Thr Ser Asp Pentylgly Ser Lys Gln  
5 Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys  
Asn-NH<sub>2</sub> [SEQ. ID. NO. 127]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
10 acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
purified in a similar way to Example 100. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
15 in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3230.4.

20

EXAMPLE 128Preparation of Peptide having SEQ ID NO. 128

Ala Gly Asp Gly Thr Phe Thr Ser Asp Pentylgly Ser Lys Gln  
25 Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys  
Asn-NH<sub>2</sub> [SEQ. ID. NO. 128]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy

acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3198.6.

#### EXAMPLE 129

##### Preparation of Peptide having SEQ ID NO. 129

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ala Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 129]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M):

calculated 3141.5.

EXAMPLE 130

Preparation of Peptide having SEQ ID NO. 130

5

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ala Lys Gln Leu  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 130]

10

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
15 purified in a similar way to Example 100. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
20 product peptide. Electrospray Mass Spectrometry (M):  
calculated 3157.5.

EXAMPLE 131

Preparation of Peptide having SEQ ID NO. 131

25

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Ala Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 131]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3100.4.

15

EXAMPLE 132Preparation of Peptide having SEQ ID NO. 132

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Ala Gln Leu  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 132]

20

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B

25

in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3157.6.

5

### EXAMPLE 133

#### Preparation of Peptide having SEQ ID NO. 133

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Ala Met  
10 Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 133]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
15 acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
purified in a similar way to Example 100. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
20 in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3100.5.

25

### EXAMPLE 134

#### Preparation of Peptide having SEQ ID NO. 134

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Ala Leu  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 134]

5           The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
10       purified in a similar way to Example 100. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
15       product peptide. Electrospray Mass Spectrometry (M):  
calculated 3100.5.

#### EXAMPLE 135

##### Preparation of Peptide having SEQ ID NO. 135

20

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Ala  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 135]

25           The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and

purified in a similar way to Example 100. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
5 is then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3154.5.

#### EXAMPLE 136

#### 10 Preparation of Peptide having SEQ ID NO. 136

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Ala  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 136]

15 The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
20 Biosystems, Inc.), cleaved from the resin, deprotected and  
purified in a similar way to Example 100. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
25 is then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3115.5.



EXAMPLE 137Preparation of Peptide having SEQ ID NO. 137

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln  
5 Pentylgly Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu  
Lys Asn-NH<sub>2</sub> [SEQ. ID. NO. 137]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
10 acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
purified in a similar way to Example 100. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
15 in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3212.4.

20

EXAMPLE 138Preparation of Peptide having SEQ ID NO. 138

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln  
25 Pentylgly Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu  
Lys Asn-NH<sub>2</sub> [SEQ. ID. NO. 138]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy

acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3173.4.

#### EXAMPLE 139

##### Preparation of Peptide having SEQ ID NO. 139

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
Ala Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 139]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3156.6.

EXAMPLE 140Preparation of Peptide having SEQ ID NO. 140

5     Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
Ala Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 140]

10     The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
purified in a similar way to Example 100. Used in analysis  
15     are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
20     calculated 3099.5.

EXAMPLE 141Preparation of Peptide having SEQ ID NO. 141

25     Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
Glu Ala Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 141]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3156.6.

#### EXAMPLE 142

#### Preparation of Peptide having SEQ ID NO. 142

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
Glu Ala Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 142]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the

product peptide. Electrospray Mass Spectrometry (M):  
calculated 3099.5.

#### EXAMPLE 143

##### 5           Preparation of Peptide having SEQ ID NO. 143

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
Glu Glu Ala Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 143]

10

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
15 Biosystems, Inc.), cleaved from the resin, deprotected and  
purified in a similar way to Example 100. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
20 is then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3156.6.

#### EXAMPLE 144

##### 25           Preparation of Peptide having SEQ ID NO. 144

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
Glu Glu Ala Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 144]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3099.5.

15

EXAMPLE 145Preparation of Peptide having SEQ ID NO. 145

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
Glu Glu Glu Ala Ala Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 145]

20

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide

25

is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3186.6.

5

EXAMPLE 146Preparation of Peptide having SEQ ID NO. 146

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
Glu Glu Glu Ala Ala Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
10 [SEQ. ID. NO. 146]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55  
15 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
20 in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3129.5.

25

EXAMPLE 147Preparation of Peptide having SEQ ID NO. 147

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Ala Leu Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 147]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3129.5.

15

EXAMPLE 148Preparation of Peptide having SEQ ID NO. 148

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
Glu Glu Glu Ala Val Ala Leu Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 148]

20

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B

25



in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3072.4.

5

EXAMPLE 149

Preparation of Peptide having SEQ ID NO. 149

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
10 Glu Glu Glu Ala Val Arg Ala Phe Ile Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 149]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
15 acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
purified in a similar way to Example 100. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
20 in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3172.5.

25

EXAMPLE 150Preparation of Peptide having SEQ ID NO. 150

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
5 Glu Glu Glu Ala Val Arg Ala Phe Ile Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 150]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
10 acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
purified in a similar way to Example 100. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
15 in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3115.5.

20

EXAMPLE 151Preparation of Peptide having SEQ ID NO. 151

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
25 Glu Glu Glu Ala Val Arg Leu Naphthylala Ile Glu Trp Leu  
Lys Asn-NH<sub>2</sub> [SEQ. ID. NO. 151]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy

acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis  
5 are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M):  
10 calculated 3266.4.

#### EXAMPLE 152

##### Preparation of Peptide having SEQ ID NO. 152

15 Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
Glu Glu Glu Ala Val Arg Leu Naphthylala Ile Glu Phe Leu  
Lys Asn-NH<sub>2</sub> [SEQ. ID. NO. 152]

The above-identified amidated peptide is assembled on  
20 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis  
25 are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M):

calculated 3209.4.

#### EXAMPLE 153

##### Preparation of Peptide having SEQ ID NO. 153

5

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Val Glu Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 153]

10

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
15 purified in a similar way to Example 100. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
20 product peptide. Electrospray Mass Spectrometry (M):  
calculated 3200.6.

#### EXAMPLE 154

##### Preparation of Peptide having SEQ ID NO. 154

25

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
Glu Glu Glu Ala Val Arg Leu Phe Val Glu Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 154]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3143.5.

15

EXAMPLE 155Preparation of Peptide having SEQ ID NO. 155

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe tButylgly Glu Trp Leu Lys  
Asn-NH<sub>2</sub> [SEQ. ID. NO. 155]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B

in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3216.5.

5

EXAMPLE 156

Preparation of Peptide having SEQ ID NO. 156

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
10 Glu Glu Glu Ala Val Arg Leu Phe tButylgly Glu Phe Leu Lys  
Asn-NH<sub>2</sub> [SEQ. ID. NO. 156]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
15 acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
purified in a similar way to Example 100. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
20 in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3159.4.

25

EXAMPLE 157Preparation of Peptide having SEQ ID NO. 157

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
5 Glu Glu Glu Ala Val Arg Leu Phe Ile Asp Trp Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 157]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
10 acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
purified in a similar way to Example 100. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
15 in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3200.6.

20

EXAMPLE 158Preparation of Peptide having SEQ ID NO. 158

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
25 Glu Glu Glu Ala Val Arg Leu Phe Ile Asp Phe Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 158]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy

acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3143.5.

#### EXAMPLE 159

##### Preparation of Peptide having SEQ ID NO. 159

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Ala Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 159]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M):



calculated 3099.5.

EXAMPLE 160

Preparation of Peptide having SEQ ID NO. 160

5

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Ala Leu Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 160]

10

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
15 purified in a similar way to Example 100. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
20 product peptide. Electrospray Mass Spectrometry (M):  
calculated 3081.4.

EXAMPLE 161

Preparation of Peptide having SEQ ID NO. 161

25

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Ala Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 161]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3172.5.

15

EXAMPLE 162Preparation of Peptide having SEQ ID NO. 162

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Ala Lys Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 162]

20

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide

25

is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3115.5.

5

EXAMPLE 163Preparation of Peptide having SEQ ID NO. 163

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Ala Asn-NH<sub>2</sub>  
[SEQ. ID. NO. 163]

10

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3157.5.

15

20

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EXAMPLE 164Preparation of Peptide having SEQ ID NO. 164

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Ala Asn-NH<sub>2</sub>

[SEQ. ID. NO. 164]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
5 acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
purified in a similar way to Example 100. Used in analysis  
10 are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3100.4.

15

#### EXAMPLE 165

##### Preparation of Peptide having SEQ ID NO. 165

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
20 Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Ala-NH<sub>2</sub>  
[SEQ. ID. NO. 165]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
25 acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
purified in a similar way to Example 100. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA

in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M):  
5 calculated 3171.6.

#### EXAMPLE 166

##### Preparation of Peptide having SEQ ID NO. 166

10 Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Ala-NH<sub>2</sub>  
[SEQ. ID. NO. 166]

The above-identified amidated peptide is assembled on  
15 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
purified in a similar way to Example 100. Used in analysis  
20 are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
25 calculated 3114.5.

EXAMPLE 167Preparation of Peptide having SEQ ID NO. 167

Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
5 Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn  
Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro-NH<sub>2</sub> [SEQ. ID. NO.  
167]

The above-identified amidated peptide is assembled on  
10 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
purified in a similar way to Example 100. Used in analysis  
15 are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
20 calculated 4033.5.

EXAMPLE 168Preparation of Peptide having SEQ ID NO. 168

His Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
25 Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn  
Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro-NH<sub>2</sub> [SEQ. ID. NO.  
168]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3984.4.

#### EXAMPLE 169

#### Preparation of Peptide having SEQ ID NO. 169

His Gly Glu Ala Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn  
Gly Gly Pro Ser Ser Gly Ala Pro Pro-NH<sub>2</sub> [SEQ. ID. NO. 169]

20

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide

is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4016.5.

5

EXAMPLE 170Preparation of Peptide having SEQ ID NO. 170

His Gly Glu Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn  
10 Gly Gly Pro Ser Ser Gly Ala Pro-NH<sub>2</sub> [SEQ. ID. NO. 170]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55  
15 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
20 in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3861.3.

25

EXAMPLE 171Preparation of Peptide having SEQ ID NO. 171

Ala Gly Glu Gly Thr Phe Thr Ser Asp Ala Ser Lys Gln Leu  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn



Gly Gly Pro Ser Ser Gly Ala Pro-NH<sub>2</sub> [SEQ. ID. NO. 171]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
5 acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
purified in a similar way to Example 100. Used in analysis  
10 are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3746.1.

15

#### EXAMPLE 172

##### Preparation of Peptide having SEQ ID NO. 172

Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
20 Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn  
Gly Gly Pro Ser Ser Gly Ala-NH<sub>2</sub> [SEQ. ID. NO. 172]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
25 acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
purified in a similar way to Example 100. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA

in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M):  
5 calculated 3742.1.

#### EXAMPLE 173

##### Preparation of Peptide having SEQ ID NO. 173

10 His Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn  
Gly Gly Pro Ser Ser Gly Ala-NH<sub>2</sub> [SEQ. ID. NO. 173]

The above-identified amidated peptide is assembled on  
15 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
purified in a similar way to Example 100. Used in analysis  
20 are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
25 calculated 3693.1.

EXAMPLE 174Preparation of Peptide having SEQ ID NO. 174

His Gly Glu Ala Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
5 Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn  
Gly Gly Pro Ser Ser Gly-NH<sub>2</sub> [SEQ. ID. NO. 174]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
10 acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
purified in a similar way to Example 100. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
15 in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3751.2.

20

EXAMPLE 175Preparation of Peptide having SEQ ID NO. 175

His Gly Glu Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Met  
25 Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn  
Gly Gly Pro Ser Ser-NH<sub>2</sub> [SEQ. ID. NO. 175]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy

acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3634.1.

#### EXAMPLE 176

##### Preparation of Peptide having SEQ ID NO. 176

Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn  
Gly Gly Pro Ser-NH<sub>2</sub> [SEQ. ID. NO. 176]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M):

calculated 3526.9.

EXAMPLE 177

Preparation of Peptide having SEQ ID NO. 177

5

His Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn  
Gly Gly Pro Ser-NH<sub>2</sub> [SEQ. ID. NO. 177]

10

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
15 purified in a similar way to Example 100. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
20 product peptide. Electrospray Mass Spectrometry (M):  
calculated 3477.9.

EXAMPLE 178

Preparation of Peptide having SEQ ID NO. 178

25

His Gly Glu Ala Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn  
Gly Gly Pro-NH<sub>2</sub> [SEQ. ID. NO. 178]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3519.9.

15

EXAMPLE 179Preparation of Peptide having SEQ ID NO. 179

His Gly Glu Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Leu  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn  
20 Gly Gly-NH<sub>2</sub> [SEQ. ID. NO. 179]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B

in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3307.7.

5

EXAMPLE 180

Preparation of Peptide having SEQ ID NO. 180

Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
10 Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn  
Gly-NH<sub>2</sub> [SEQ. ID. NO. 180]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
15 acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis.  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
20 in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3186.5.

25

EXAMPLE 181

Preparation of Peptide having SEQ ID NO. 181

His Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn  
Gly Gly tPro Ser Ser Gly Ala tPro tPro tPro-NH<sub>2</sub> [SEQ. ID.  
NO. 181]

5

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
10 Biosystems, Inc.), cleaved from the resin, deprotected and  
purified in a similar way to Example 100. Double couplings  
are required at residues 37,36 and 31. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
15 in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 4121.1.

20

#### EXAMPLE 182

##### Preparation of Peptide having SEQ ID NO. 182

His Gly Glu Ala Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn  
Gly Gly Pro Ser Ser Gly Ala tPro tPro tPro-NH<sub>2</sub> [SEQ. ID.  
25 NO. 182].

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55



mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Double couplings are required at residues 37, 36 and 31. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4173.2.

#### EXAMPLE 183

##### Preparation of Peptide having SEQ ID NO. 183

His Gly Glu Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn  
Gly Gly NMeala Ser Ser Gly Ala NMeala NMeala-NH<sub>2</sub> [SEQ. ID.  
NO. 183]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Compound 1. Double couplings are required at residues 36 and 31. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is

then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3796.1.

5

EXAMPLE 184Preparation of Peptide having SEQ ID NO. 184

Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn  
10 Gly Gly hPro Ser Ser Gly Ala hPro-NH<sub>2</sub> [SEQ. ID. NO. 184]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55  
15 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. A double coupling is required at residue 31. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in  
20 ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3871.1.

25

EXAMPLE 185Preparation of Peptide having SEQ ID NO. 185

His Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
5 Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn  
Gly Gly Pro Ser Ser Gly Ala-NH<sub>2</sub> [SEQ. ID. NO. 185]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
10 acetamide norleucine MBHA resin (Novabiochem, 0.55  
mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
purified in a similar way to Example 100. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
15 in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 3750.2.

20

EXAMPLE 186Preparation of Peptide having SEQ ID NO. 186

His Gly Asp Ala Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
25 Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn  
Gly Gly-NH<sub>2</sub> [SEQ. ID. NO. 186]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy

acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3408.8.

#### EXAMPLE 187

##### Preparation of Peptide having SEQ ID NO. 187

Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn  
Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser-NH<sub>2</sub> [SEQ. ID.  
NO. 187]

The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the

product peptide. Electrospray Mass Spectrometry (M):  
calculated 4120.6.

#### EXAMPLE 188

##### 5                    Preparation of Peptide having SEQ ID NO. 188

Ala Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu  
Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn  
Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser-NH<sub>2</sub> [SEQ. ID.  
10                    NO. 188]

The above-identified amidated peptide is assembled on  
4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy  
acetamide norleucine MBHA resin (Novabiochem, 0.55  
15                    mmole/g) using Fmoc-protected amino acids (Applied  
Biosystems, Inc.), cleaved from the resin, deprotected and  
purified in a similar way to Example 100. Used in analysis  
are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA  
in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B  
20                    in Solvent A over 30 minutes) of the lyophilized peptide  
is then carried out to determine the retention time of the  
product peptide. Electrospray Mass Spectrometry (M):  
calculated 4005.5.

##### 25                    EXAMPLE 189

Preparation of C-terminal carboxylic acid peptides  
corresponding to the above C-terminal amide sequences for  
Peptides having SEQ ID NOS. 100-166, 172-177, 179-180 and  
185-188.

C-terminal carboxylic acid peptides corresponding to amidated having SEQ ID NOS. 100-166, 172-177, 179-180 and 185-188 are assembled on the so called Wang resin (p-alkoxybenzylalcohol resin (Bachem, 0.54 mmole/g)) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to that described in Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry provides an experimentally determined (M).

15

#### EXAMPLE 190

Preparation of C-terminal carboxylic acid peptides corresponding to the above C-terminal amide sequences for  
Peptides having SEQ ID NOS. 167-171, 178 and 181-184.

20

C-terminal carboxylic acid peptides corresponding to amidated SEQ ID NOS. 167-171, 178 and 181-184 are assembled on the 2-chlorotriethylchloride resin (200-400 mesh), 2% DVB (Novabiochem, 0.4-1.0 mmole/g)) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to that described in Example 100. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in

25

ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry provides  
5 an experimentally determined (M).

Various modifications of the invention in addition to those shown and described herein will become apparent to  
10 those skilled in the art from the foregoing description and fall within the scope of the following claims.

WE CLAIM:

1. A method for treating conditions or disorders which can be alleviated by reducing food intake in a subject comprising administering to said subject a  
5 therapeutically effective amount of an exendin or an exendin agonist.
2. The method according to claim 1 wherein said exendin or exendin agonist is administered parenterally.
3. The method according to claim 2 wherein said  
10 parenteral administration is by injection.
4. The method according to claim 3 wherein the injection is a peripheral injection.
5. The method according to claim 1 wherein about 10  $\mu$ g-30 $\mu$ g to about 5mg of the exendin or exendin agonist is  
15 administered per day.
6. The method according to claim 1 wherein about 10  $\mu$ g-30  $\mu$ g to about 2 mg of the exendin or exendin agonist is administered per day.
7. The method according to claim 1, wherein about 30  
20  $\mu$ g to about 500  $\mu$ g of the exendin or exendin agonist is administered per day.
8. The method of claim 1 wherein said condition or disorder is obesity.
9. The method of claim 1 wherein said condition or  
25 disorder is Type II diabetes.
10. The method of claim 1 wherein said subject is human.
11. The method of claim 1 wherein said condition or disorder is an eating disorder.



12. The method of claim 1 wherein said condition or disorder is insulin-resistance syndrome.

13. A method for reducing the appetite of a subject comprising administering to said subject an appetite-  
5 lowering amount of an exendin or an exendin agonist.

14. A method for reducing the weight of a subject comprising administering to said subject a therapeutically effective amount of an exendin or an exendin agonist.

15. A method for lowering plasma lipids comprising  
10 administering to said subject a therapeutically effective amount of an exendin or an exendin agonist.

16. The method according to any of claims 1-15 wherein said exendin is exendin-3.

17. The method according to any of claims 1-15  
15 wherein said exendin is exendin-4.

18. The method according to any of claims 1-15 wherein said exendin agonist is selected from the group consisting of exendin-4 (1-30), exendin-4 (1-30) amide, exendin-4 (1-28) amide, <sup>14</sup>Leu, <sup>25</sup>Phe exendin-4 amide, <sup>14</sup>Leu, <sup>25</sup>Phe exendin-4 (1-28) amide, and <sup>14</sup>Leu, <sup>22</sup>Ala, <sup>25</sup>Phe  
20 exendin-4 (1-28) amide.

19. The method according to any of claims 1-15, further comprising administering a therapeutically effective amount of one or more compounds selected from the  
25 group consisting essential of an amylin agonist, a leptin, and a CCK.

20. The method according to any of claims 1-15 wherein said exendin agonist is an exendin agonist according to Formula I.

21. The method according to any of claims 1-15 wherein said exendin agonist is an exendin agonist according to Formula II.

5 22. The method according to any of claims 1-15 wherein said exendin agonist is an exendin agonist according to Formula III.

23. A pharmaceutical composition for use in the treatment of conditions or disorders associated with hypernutrition comprising a therapeutically effective  
10 amount of an exendin or exendin agonist in association with a pharmaceutically acceptable carrier.

24. The pharmaceutical composition according to claim 21, wherein said exendin is exendin-3.

25. The pharmaceutical composition according to claim  
15 21 wherein said exendin is exendin-4.

26. The pharmaceutical composition according to claim 21 wherein said exendin agonist is selected from the group consisting of exendin-4 (1-30), exendin-4 (1-30) amide, exendin-4 (1-28) amide, <sup>14</sup>Leu,<sup>25</sup>Phe exendin-4 amide,  
20 <sup>14</sup>Leu,<sup>25</sup>Phe exendin-4 (1-28) amide, and <sup>14</sup>Leu,<sup>22</sup>Ala,<sup>25</sup>Phe exendin-4 (1-28) amide.

27. The pharmaceutical composition of claim 21 wherein said therapeutically effective amount is a therapeutically effective amount for a human subject.

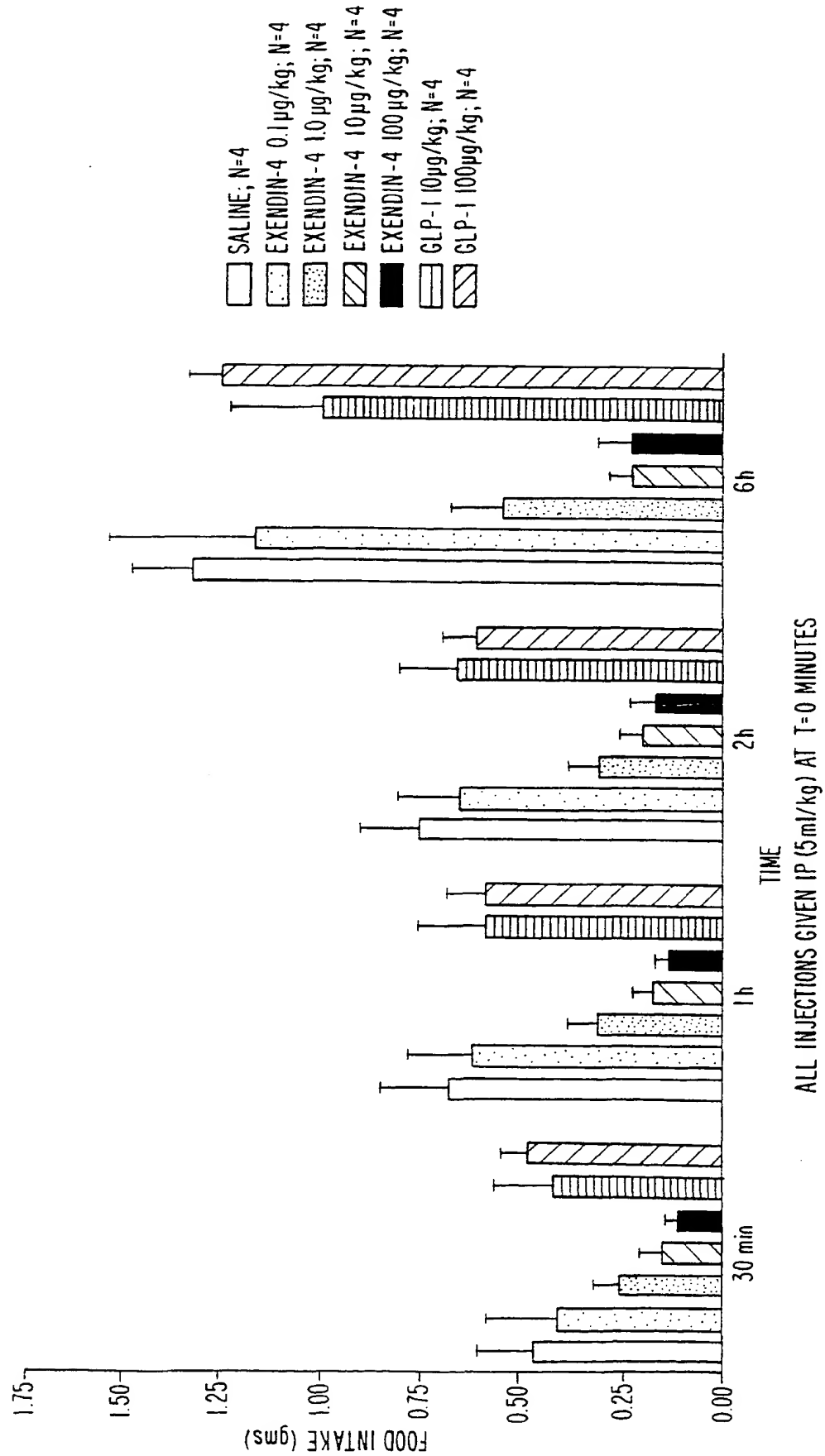
25 28. A pharmaceutical composition for use in reducing the appetite of a subject comprising a therapeutically effective amount of an exendin or exendin agonist in association with a pharmaceutically acceptable carrier.

29. A pharmaceutical composition for use in reducing the weight of a subject comprising a therapeutically effective amount of an exendin or exendin agonist in association with a pharmaceutically acceptable carrier.

5        30. A pharmaceutical composition for use in lowering the plasma lipid level of a subject comprising a therapeutically effective amount of an exendin or exendin agonist in association with a pharmaceutically acceptable carrier.

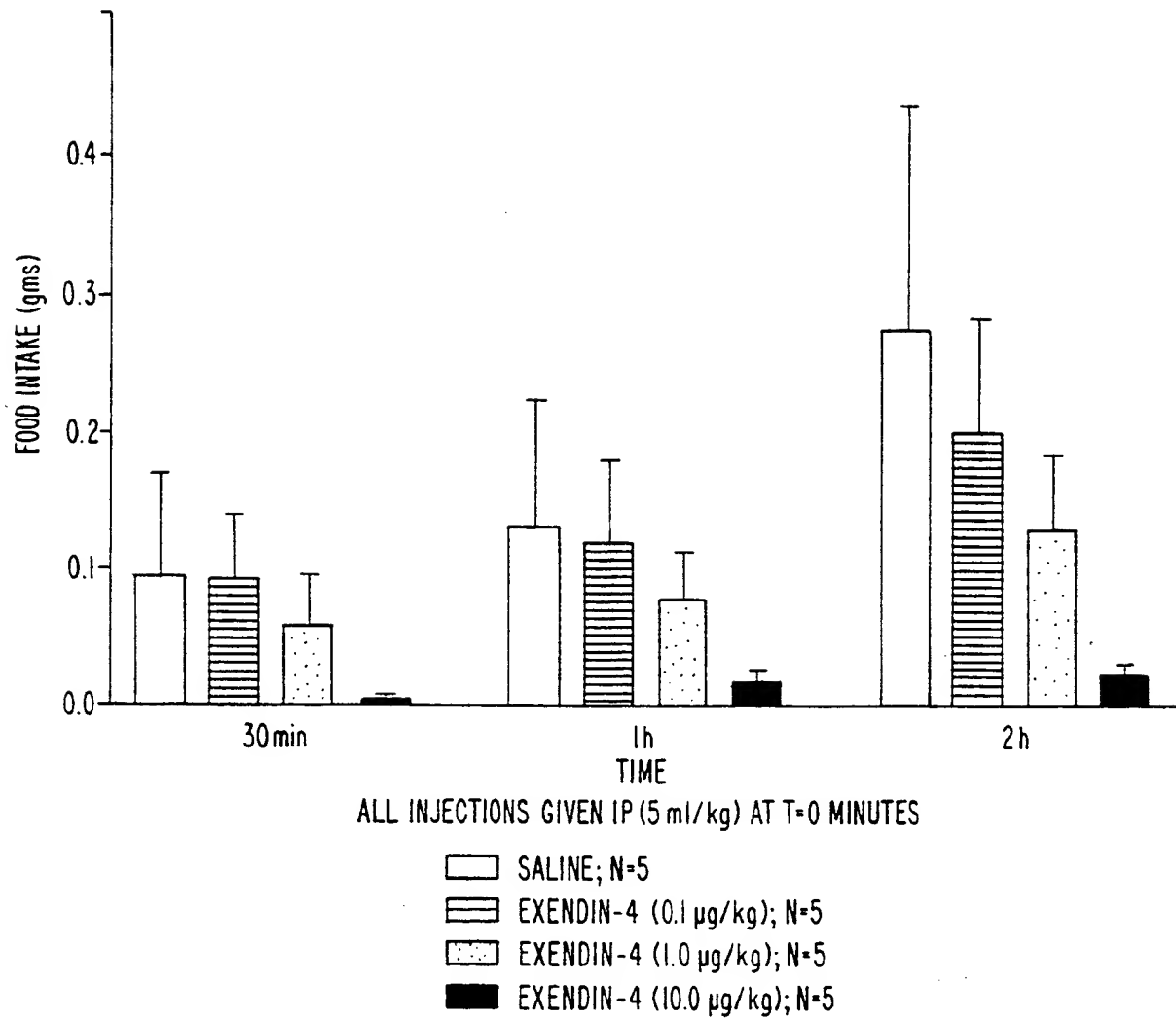
10       31. The pharmaceutical composition according to any of claims 21-28, further comprising a therapeutically effective amount of one or more compounds selected from the group consisting essentially of an amylin agonist, a leptin, and a CCK.

FIG. 1.



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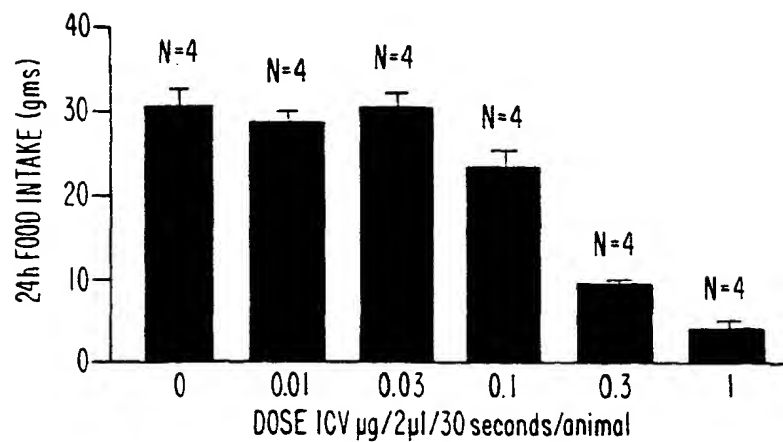
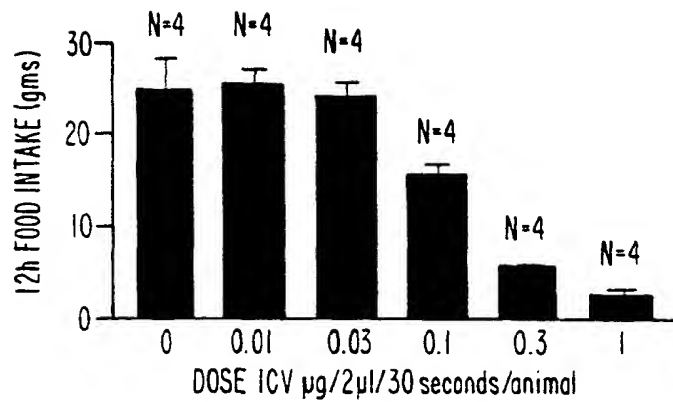
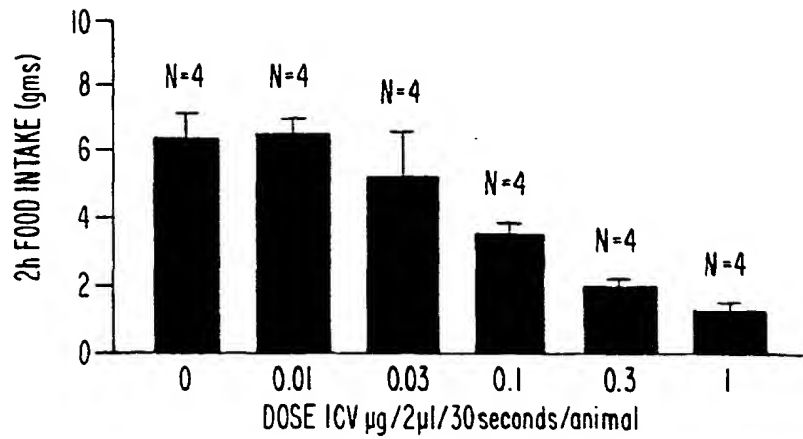
FIG. 2.



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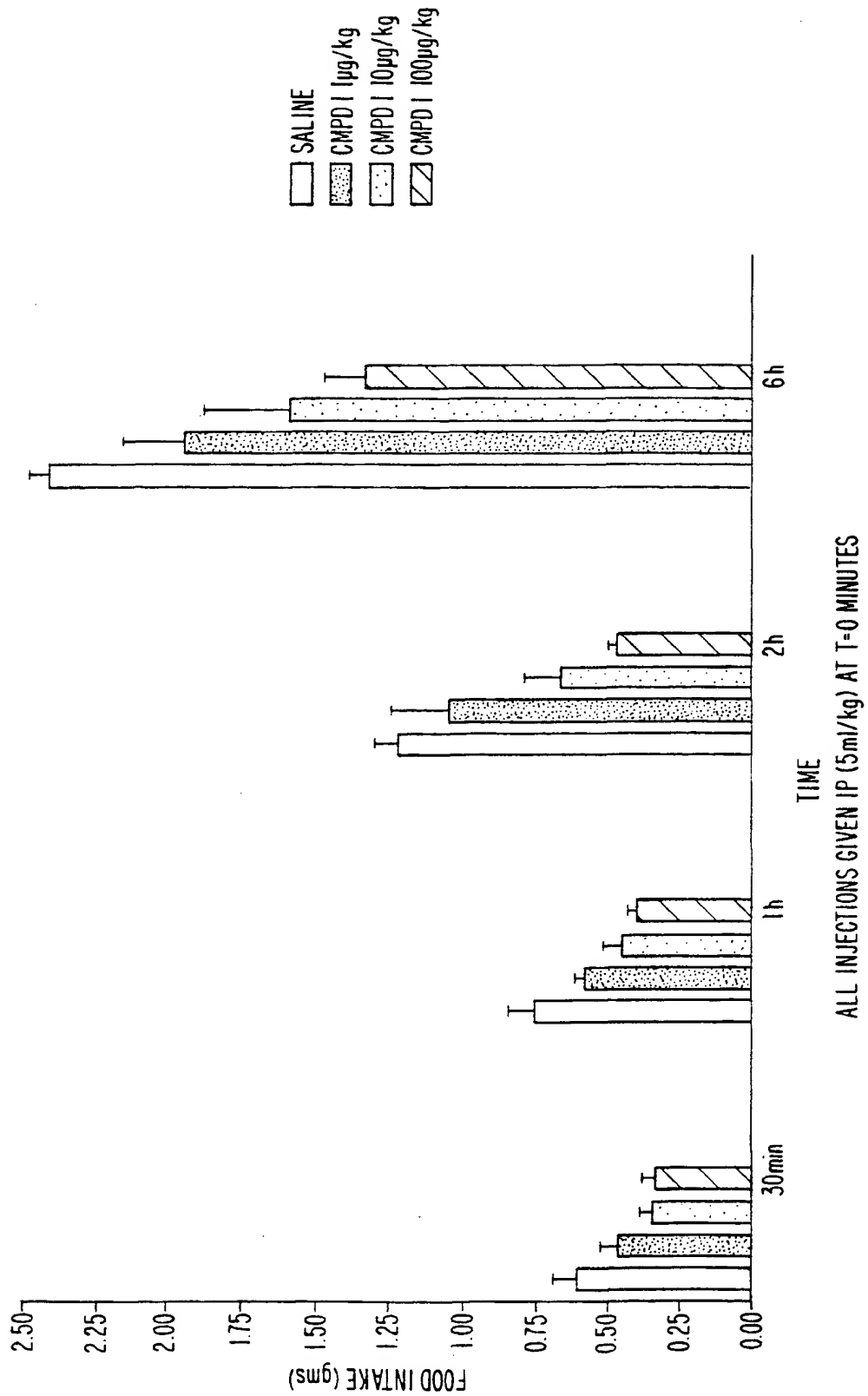
FIG. 3.



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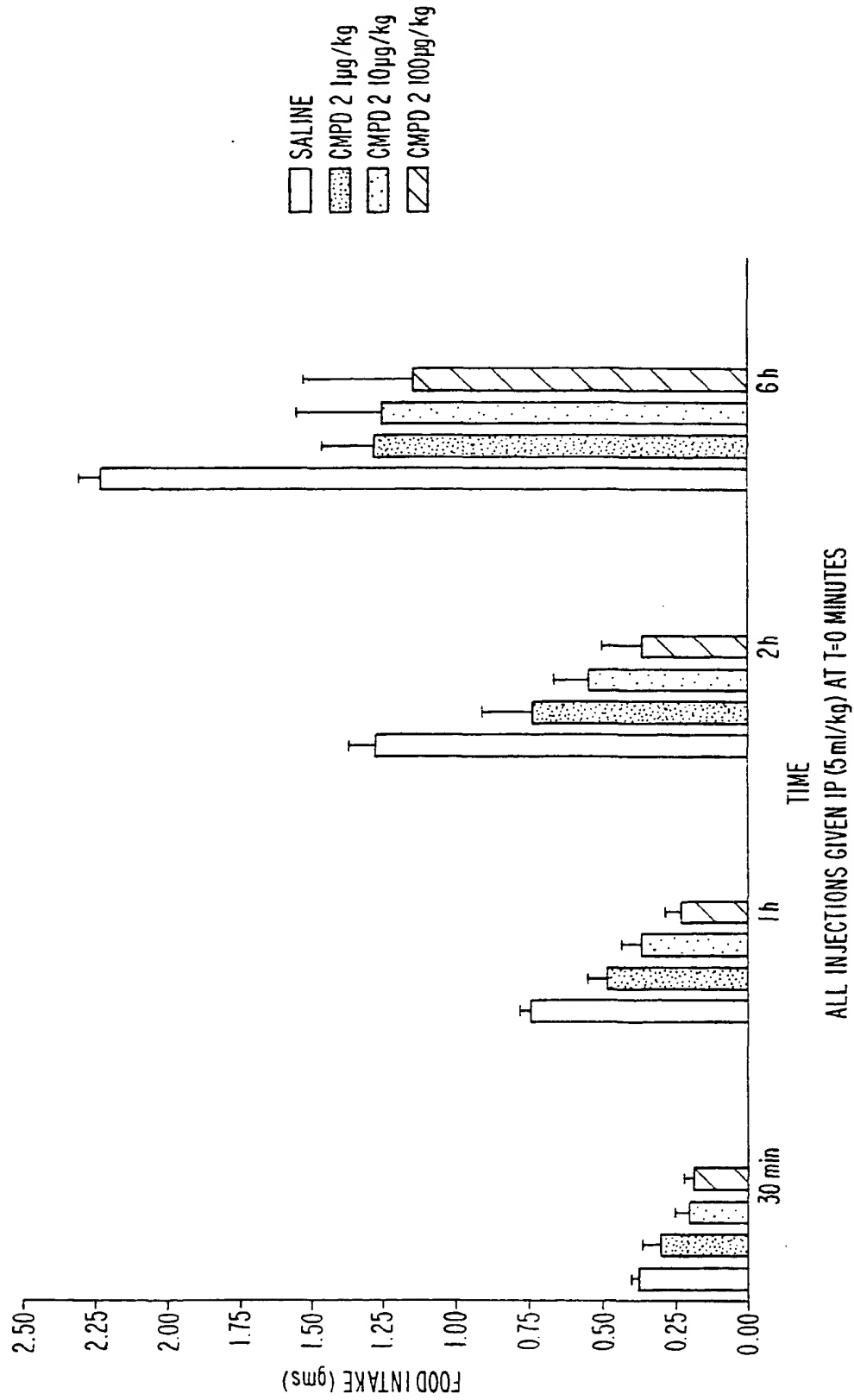
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FIG. 4.



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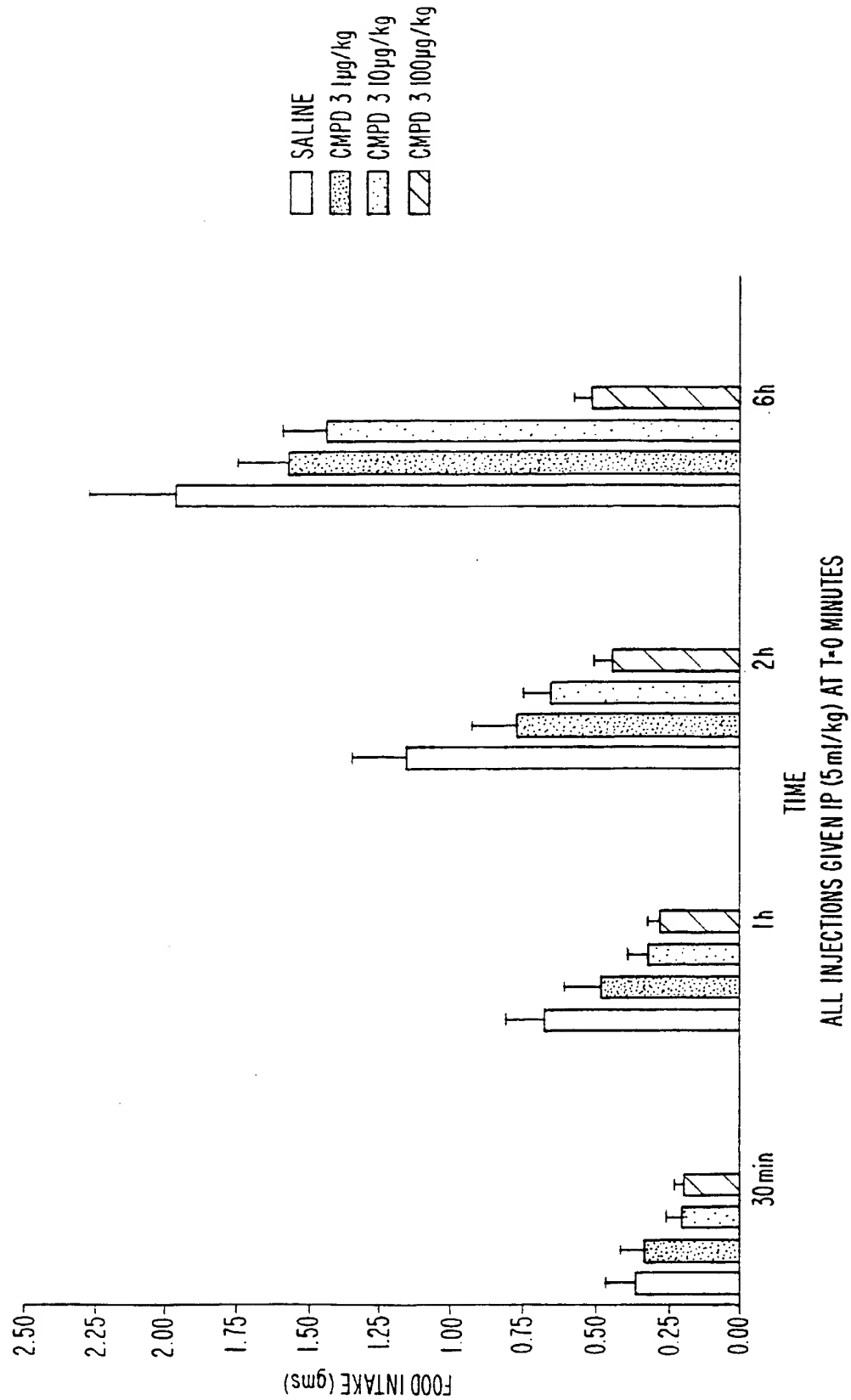
FIG. 5.





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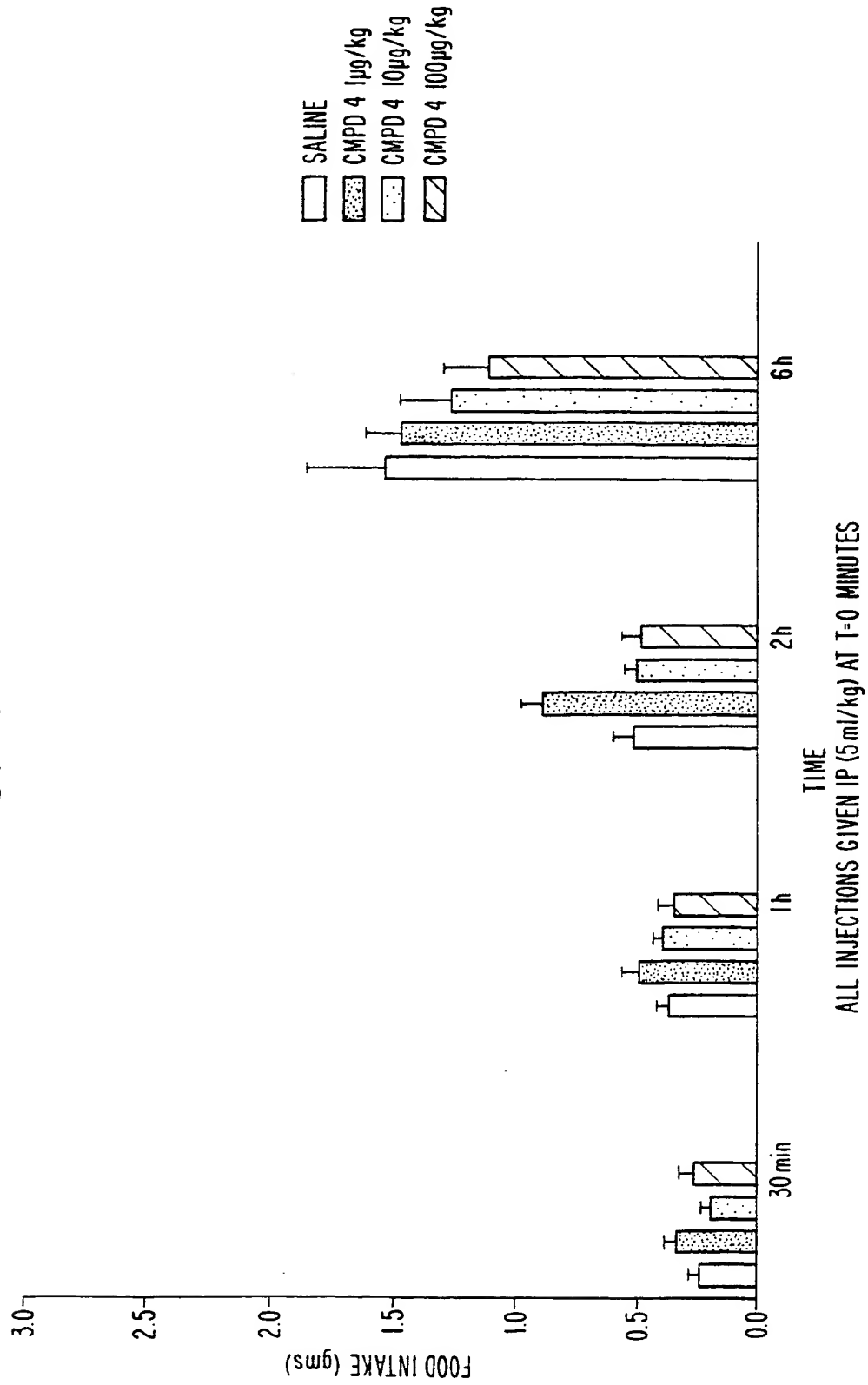
FIG. 6.



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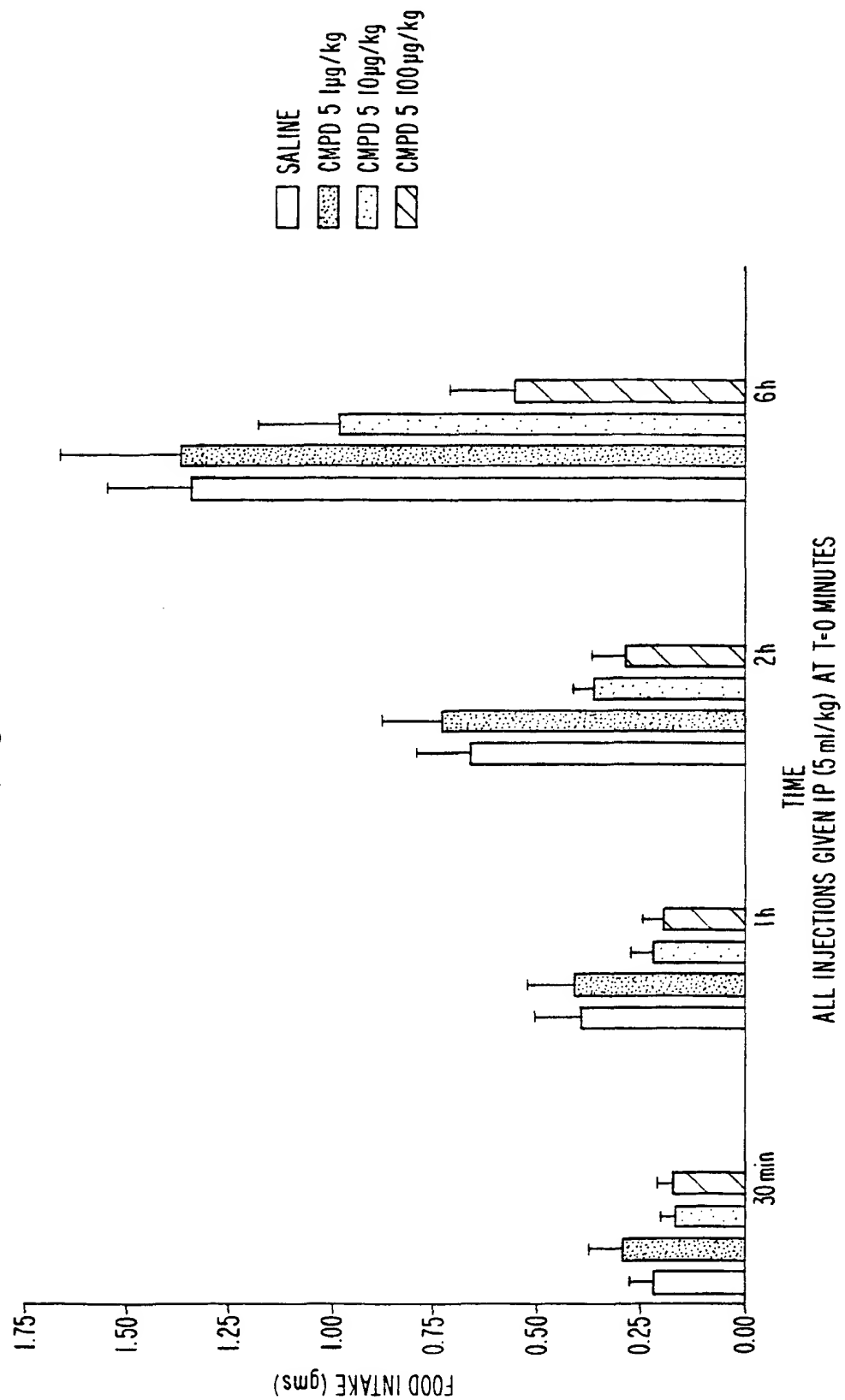
FIG. 7.



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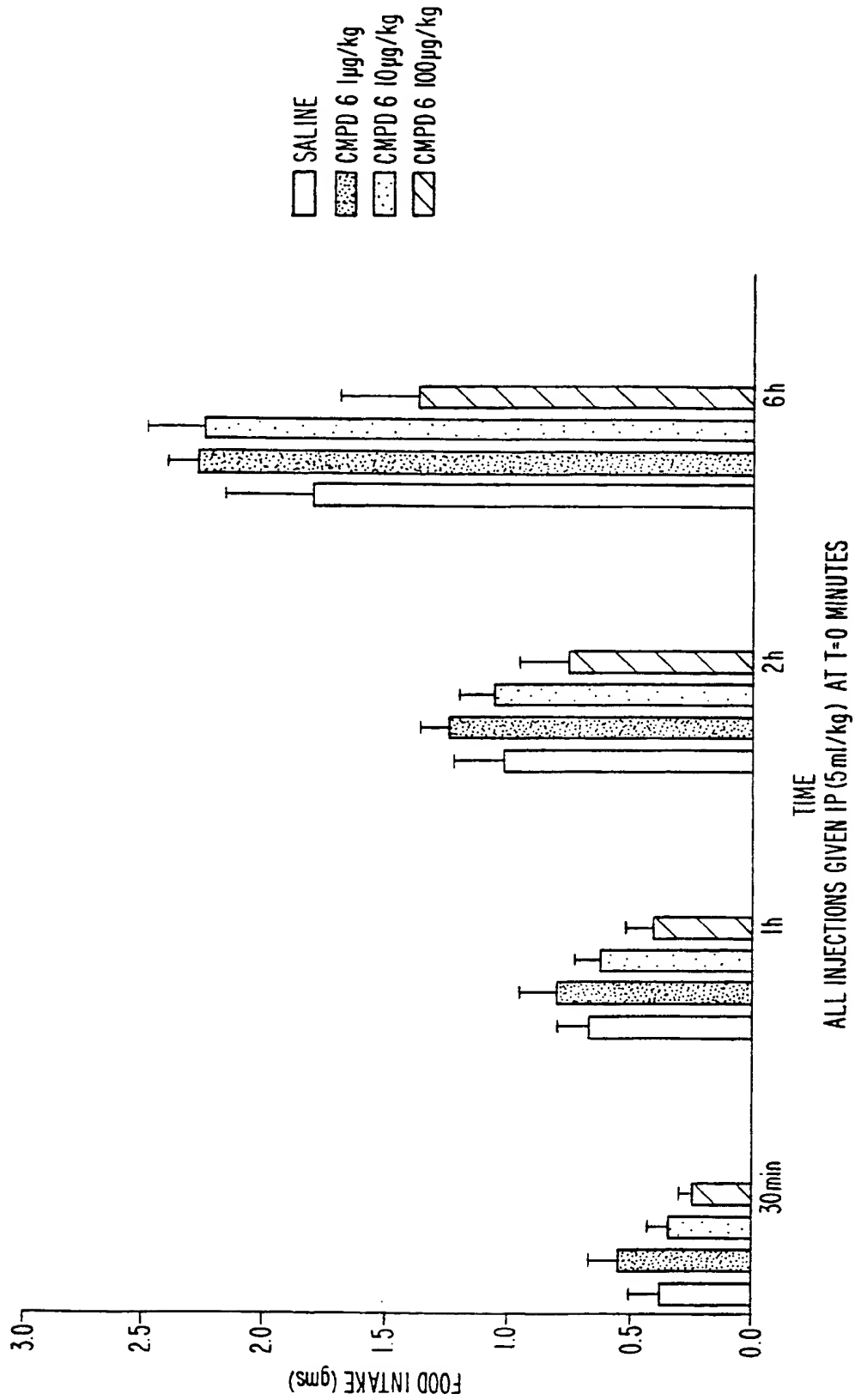
FIG. 8.



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FIG. 9.



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1 15 20  
 Xaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub> Gly Thr Xaa<sub>4</sub> Xaa<sub>5</sub> Xaa<sub>6</sub> Xaa<sub>7</sub> Xaa<sub>8</sub> Ser Lys Gln Xaa<sub>9</sub> Glu Glu Ala Val Arg Leu  
 25 30 35  
 Xaa<sub>10</sub> Xaa<sub>11</sub> Xaa<sub>12</sub> Xaa<sub>13</sub> Leu Lys Asn Gly Gly Xaa<sub>14</sub> Ser Ser Gly Ala Xaa<sub>15</sub> Xaa<sub>16</sub> Xaa<sub>17</sub> Xaa<sub>18</sub>-Z

(SEQ. ID. NO.)	Xaa <sub>1</sub>	Xaa <sub>2</sub>	Xaa <sub>3</sub>	Xaa <sub>4</sub>	Xaa <sub>5</sub>	Xaa <sub>6</sub>	Xaa <sub>7</sub>	Xaa <sub>8</sub>	Xaa <sub>9</sub>	Xaa <sub>10</sub>	Xaa <sub>11</sub>	Xaa <sub>12</sub>	Xaa <sub>13</sub>	Xaa <sub>14</sub>	Xaa <sub>15</sub>	Xaa <sub>16</sub>	Xaa <sub>17</sub>	Xaa <sub>18</sub>	Z
9	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Leu	Phe	Ile	Glu	Phe	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
10	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Leu	Phe	Ile	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
11	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	Ile	Glu	Phe	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
12	Tyr	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	Ile	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
13	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	Ile	Glu	Trp	Pro	Pro	Pro	Pro	Tyr	NH <sub>2</sub>
14	His	Gly	Asp	Phe	Thr	Ser	Asp	Leu	Met	Phe	Ile	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
15	His	Gly	Glu	naph	Thr	Ser	Asp	Leu	Met	Phe	Ile	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
16	His	Gly	Glu	Phe	Ser	Ser	Asp	Leu	Met	Phe	Ile	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
17	His	Gly	Glu	Phe	Ser	Thr	Asp	Leu	Met	Phe	Ile	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
18	His	Gly	Glu	Phe	Thr	Thr	Asp	Leu	Met	Phe	Ile	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
19	His	Gly	Glu	Phe	Thr	Ser	Glu	Leu	Met	Phe	Ile	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
20	His	Gly	Glu	Phe	Thr	Ser	Asp	pGly	Met	Phe	Ile	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
21	His	Gly	Glu	Phe	Thr	Ser	Asp	pGly	Leu	Phe	Ile	Glu	Phe	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
22	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	pGly	Phe	Ile	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>

**FIGURE 10**  
 (Sheet 1 of 2)

[SEQ. ID. NO.]	Xaa <sub>1</sub>	Xaa <sub>2</sub>	Xaa <sub>3</sub>	Xaa <sub>4</sub>	Xaa <sub>5</sub>	Xaa <sub>6</sub>	Xaa <sub>7</sub>	Xaa <sub>8</sub>	Xaa <sub>9</sub>	Xaa <sub>10</sub>	Xaa <sub>11</sub>	Xaa <sub>12</sub>	Xaa <sub>13</sub>	Xaa <sub>14</sub>	Xaa <sub>15</sub>	Xaa <sub>16</sub>	Xaa <sub>17</sub>	Xaa <sub>18</sub>	Z
23	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	pGly	Phe	Ile	Glu	Phe	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
24	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	naph	Ile	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
25	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	Val	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
26	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Leu	Phe	Val	Glu	Phe	Pro	Pro	Pro	Pro	Ser	NH
27	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	tBuG	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
28	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Leu	Phe	tBuG	Glu	Phe	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
29	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	Ile	Asp	Trp	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
30	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	Ile	Glu	Phe	Pro	Pro	Pro	Pro	Ser	NH <sub>2</sub>
31	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	Ile	Glu	Trp	tPro	tPro	tPro	tPro	Ser	NH <sub>2</sub>
32	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	Ile	Glu	Trp	Pro	tPro	tPro	tPro	Ser	NH <sub>2</sub>
33	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	Ile	Glu	Trp	hPro	hPro	hPro	hPro	Ser	NH <sub>2</sub>
34	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	Ile	Glu	Trp	Pro	hPro	hPro	hPro	Ser	NH <sub>2</sub>
35	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Leu	Phe	Ile	Glu	Phe	tPro	tPro	tPro	tPro	Ser	NH <sub>2</sub>
36	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Leu	Phe	Ile	Glu	Phe	hPro	hPro	hPro	hPro	Ser	NH <sub>2</sub>
37	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	Ile	Glu	Trp	MeAla	MeAla	MeAla	MeAla	Ser	NH
38	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	Ile	Glu	Trp	Pro	MeAla	MeAla	MeAla	Ser	NH
39	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Leu	Phe	Ile	Glu	Phe	MeAla	MeAla	MeAla	MeAla	Ser	NH

**FIGURE 10**  
(Sheet 2 of 2)

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/00449

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 38/16

US CL : 514/2, 866

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/2, 866

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
NONEElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
CAS ONLINE, MEDLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,424,286 A (ENG) 13 June 1995 see entire document.	1-31

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

07 MAY 1998

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